



# STIC Search Report

## EIC 3700

STIC Database Tracking Number: 126096

TO: Linh T Truong  
Location: cp2 3b30  
Art Unit: 3761  
Tuesday, July 06, 2004

Case Serial Number: 10/035059

From: Emory Damron  
Location: EIC 3700  
CP2-2C08  
Phone: 305-8587

[Emory.Damron@uspto.gov](mailto:Emory.Damron@uspto.gov)

### Search Notes

Dear Linh,

Please find below an inventor search in the bibliographic and full-text foreign patent files, as well as keyword searches in the patent and non-patent literature files, both bibliographic and full text.

References of potential pertinence have been tagged, but please review all the packets in case you like something I didn't.

In addition to searching on Dialog, I also searched Google.com, EPO/JPO/Derwent, and STN/CAS.

Almost all of relevant art I found was patent literature, and assigned to Procter and Gamble. (I believe the inventor works for Kimberly-Clark).

Please contact me if I can refocus or expand any aspect of this case, and please take a moment to provide any feedback (on the form provided) so EIC 3700 may better serve your needs.

Sincerely,

Emory Damron

Technical Information Specialist

EIC 3700, US Patent & Trademark Office

Phone: (703) 305-8587/ Fax: (703) 306-5915

[Emory.damron@uspto.gov](mailto:Emory.damron@uspto.gov)



Access DB# 126096

## SEARCH REQUEST FORM

## Scientific and Technical Information Center

Requester's Full Name: Linh Truong Examiner #: 78961 Date: 6/30/04  
Art Unit: 3761 Phone Number 30 605-4974 Serial Number: 101035, 659  
Mail Box and Bldg/Room Location: \_\_\_\_\_ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Bandage, methods of producing and using same  
Inventors (please provide full names): Sohail Malik

Earliest Priority Filing Date: 12/28/2001

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Compounds Chitosan niacinamide ascorbate salt  
and/or ascorbate salt

- used in wound healing  
used in layers of dressings  
or bandages

## STAFF USE ONLY

	Type of Search	Vendors and cost where applicable
Searcher: <u>DAMRON, EMORY</u>	NA Sequence (#) _____	STN <u>X</u> <u>35.81</u>
Searcher Phone #: <u>305 8587</u>	AA Sequence (#) _____	Dialog <u>X</u> <u>445.31</u>
Searcher Location: <u>CP2 208</u>	Structure (#) _____	Questel/Orbit _____
Date Searcher Picked Up: <u>7/2/04</u>	Bibliographic <u>X</u>	Dr.Link _____
Date Completed: <u>7/6/04 noon</u>	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: <u>145m</u>	Fulltext <u>X</u>	Sequence Systems _____
Clerical Prep Time: <u>0</u>	Patent Family _____	WWW/Internet <u>X</u>
Online Time: <u>145m</u>	Other _____	Other (specify) _____

Set	Items	Description
S1	660244	BANDAG? OR GAUZ? OR COMFEEL? OR PATCH? OR DRESSING? OR COM-PRESS?? OR BANDOID? OR BAND() (AID OR AIDS) OR PAD OR PADS
S2	726888	MAIM? OR SCRATCH? OR SCRAP? OR ABRASION? OR TRAUMA? OR INJ-UR? OR WOUND? OR LACERAT? OR BURN? OR IRRITATION?
S3	12327	CHITOSAN? OR C8H13NO5 OR "1398-61-4" OR 1398()61()4 OR CHI-TIN OR CHITINDEACETYLAT? OR GLUCOSAMINE(3N)POLYSACCHARID? OR -ACHITIN OR ACETYL?(2N)GLUCOSAMIN?
S4	18151	(ASCORBAT? OR ASCORBIC?) (2N) (SALT? OR ACID? OR SODIUM? OR -MINERAL? OR CALCIUM? OR MANGANES? OR MAGNESIUM?) OR VITAMINC -OR VITAMIN()C OR C6H8O6 OR "50-81-7" OR 50()81()7
S5	9678	NIACINAMID? OR NIACIN? OR NICOTINIC()ACID? OR NICOTINAMID? OR C6H5N2O OR C6H6N2O OR "98-92-0" OR 98()92()0 OR "59-67-6" -OR 59()67()6 OR (PYREDENE? OR PYRIDINE?) (2N) (CARBOXYLIC? OR C-ARBOXAMID?) OR VITAMINB3 OR VITAMIN()B3
S6	493220	HEAL? OR CURE?? OR CURING OR SKIN? OR DERMA? OR DERMI? OR -DERME? OR DERMO?
S7	103651	IC=A61F?
S8	34204	S1 AND S2
S9	660244	S8 OR S1
S10	39	S3 AND S4 AND S5
S11	34	S10 AND S6:S7
S12	7	S10:S11 AND S9
S13	7	IDPAT (sorted in duplicate/non-duplicate order)

? show files

File 347:JAPIO Nov 1976-2004/Feb(Updated 040607)

(c) 2004 JPO & JAPIO

File 350:Derwent WPIX 1963-2004/UD,UM &UP=200442

(c) 2004 Thomson Derwent

13/3,K/1 (Item 1 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
(c) 2004 Thomson Derwent. All rts. reserv.

015922427 \*\*Image available\*\*  
WPI Acc No: 2004-080267/200408  
XRAM Acc No: C04-032928  
XRPX Acc No: N04-064103

*APPLICATION*

**Adhesive bandage for treating acute wounds , burn wounds , and irritations , includes adhesive layer, absorbent layer, and wound healing antimicrobial agent and hemostatic agent**

Patent Assignee: KIMBERLY-CLARK WORLDWIDE INC (KIMB )

Inventor: MALIK S

Number of Countries: 101 Number of Patents: 003

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
US 20030125654	A1	20030703	US 200135059	A	20011228	200408 B
WO 200357265	A1	20030717	WO 2002US29813	A	20020918	200408
AU 2002327666	A1	20030724	AU 2002327666	A	20020918	200421

Priority Applications (No Type Date): US 200135059 A 20011228

Patent Details:

Patent No	Kind	Lan Pg	Main IPC	Filing Notes
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US 20030125654	A1	18	A61F-013/00	
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WO 200357265	A1 E		A61L-015/44	
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Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

AU 2002327666	A1		A61L-015/44	Based on patent WO 200357265
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**Adhesive bandage for treating acute wounds , burn wounds , and irritations , includes adhesive layer, absorbent layer, and wound healing antimicrobial agent and hemostatic agent**

Abstract (Basic):

... An adhesive bandage comprises a layer including top and bottom surfaces (75, 76), an adhesive layer (77), an absorbent layer (80) for absorbing exudates from the wound site, a layer for allowing limited flow of exudates from the wound site, and a wound healing antimicrobial agent and/or a hemostatic agent (90), or a single wound healing agent with antimicrobial and hemostatic functionality.

... An adhesive bandage comprises a first layer for covering a wound site and an area around the wound site, the first layer including top and bottom surfaces; a second adhesive layer on the first layer bottom surface, for adhering the adhesive bandage to a wound site; a third absorbent layer on the second layer, for absorbing exudates from the wound site; a fourth layer on the third absorbent layer for allowing limited flow of exudates from the wound site to the third layer; and a wound healing antimicrobial agent and a hemostatic agent, or a single wound healing agent with antimicrobial and hemostatic functionality, each agent associated with the adhesive bandage in a position where the agent will come in contact with the wound site, and which are transferable from the adhesive bandage to the wound site...

...An INDEPENDENT CLAIM is also included for a method of producing an adhesive bandage comprising providing an adhesive bandage ; and

treating either the absorbent layer and/or the fourth layer, to include a wound healing hemostatic agent and an antimicrobial agent or a single wound healing agent with hemostatic and antimicrobial multifunctionality, which agents are transferable from the adhesive bandage to the wound site...

...The invention is used for treating acute wounds , burn wounds , and irritations (all claimed...

...does not utilize agents that may cause an allergic response to certain individuals, but promotes wound healing .

...

...The figure shows an exploded view of the bandage .

...

... Wound healing antimicrobial agent and a hemostatic agent (90 Technology Focus:

... Preferred Component: The wound healing antimicrobial agent and the hemostatic agent are located in a coating layer over the fourth

...

...Preferred Component: The antimicrobial, hemostatic, and single multifunctional wound healing agents comprise niacinamide ascorbate, chitosan , and/or preferably chitosan niacinamide ascorbate salt .

...Title Terms: BANDAGE ; .

International Patent Class (Main): A61F-013/00 ...

13/3,K/2 (Item 2 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
(c) 2004 Thomson Derwent. All rts. reserv.

015685839 \*\*Image available\*\*  
WPI Acc No: 2003-748028/200370  
XRAM Acc No: C03-204943

Adhesive patch used to deliver pharmaceutical and cosmetic agents to skin surface of human, comprises cosmetic formulation having cosmetic agent, solvent, skin absorption enhancer, and pressure sensitive adhesive and polymer

Patent Assignee: LECTEC CORP (LECT-N); BUSEMAN T (BUSE-I); COOKE D (COOK-I); ROLF D (ROLF-I)

Inventor: BUSEMAN T; COOKE D; ROLF D

Number of Countries: 102 Number of Patents: 003

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200363817	A1	20030807	WO 2003US2425	A	20030128	200370 B
US 20030152610	A1	20030814	US 200260060	A	20020128	200370
AU 2003210678	A1	20030902	AU 2003210678	A	20030128	200422

LATE  
DATE

Priority Applications (No Type Date): US 200260060 A 20020128

Patent Details:

Patent No Kind Lan Pg Main IPC Filing Notes

WO 200363817 A1 E 76 A61K-007/48

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW

US 20030152610 A1 A61K-009/70

AU 2003210678 A1 A61K-007/48 Based on patent WO 200363817

Adhesive patch used to deliver pharmaceutical and cosmetic agents to skin surface of human, comprises cosmetic formulation having cosmetic agent, solvent, skin absorption enhancer, and pressure sensitive adhesive and polymer

Abstract (Basic):

... An adhesive patch (1) has flexible backing (2) having front and back sides (4); and cosmetic formulation having cosmetic agent, solvent, skin absorption enhancer, and pressure sensitive adhesive and polymer. The formulation is on a portion of...

... a person's face such that the front side of the backing adhesively attaches to skin surface of the person's face near the eyes, and the second portion having an...

...the person's face such that the front side of the backing adhesively attaches to skin surface of the person's face near the mouth...

... Dermatological .

...The patch is used to deliver pharmaceutical and cosmetic agents to skin surface of human. It is used to improve appearance of wrinkles, to exfoliate skin surface of mammals, to hydrolyze the skin surface, and for firming the skin surface (claimed...

...The **patch** has high degree of penetration of the formulation in the backing. It is convenient, safe...

...The figure illustrates specific adhesive **skin patch** .

...

...Adhesive **patch** (1

Technology Focus:

... Preferred Compounds: The polymer includes quat. ammonium salt, gum tragacanth, gum Ghatti, gum agar, pectin, **chitin** and its derivative, carrageenan, calcium cross-linked alginate, cross-linked polymer by boron or di...

...lecithin, diethylene glycol ethyl ether, diethylene glycol ethyl ether acetate and/or their salts. The **skin** absorption enhancer is diethylene glycol monoethyl ether, dimethyl sulfoxide (DMSO), C10 DMSO, ionic surfactants, nonThe **patch** further comprises a preservative (0.01-1.5 wt% of the formulation) selected from e...

...The **patch** further comprises one or more **skin** conditioners/ **skin** protectants (up to 2 wt% of the formulation), selected from e.g. alpha-hydroxy acid...

...cranberry seed oil, green tea, white tea, methyl paraben, propylparaben, caffeine, xanthine, vitamin B-3, **nicotinamide** , licorice, calamine, aluminum hydroxide gel, cocoa butter, aloe or lanolin...

...scavenger consisting of lycopene, tumeric, green tea, white tea, alpha-hydroxy acid, beta-hydroxy acid, **Vitamin C** , Vitamin E, Vitamin A, their salts, or their derivatives. It is a collagen synthesis stimulator...

...or collagen cross-linking inhibitor. The collagen synthesis stimulator is a plant extract containing keratin, **vitamin C** , and/or copper containing peptide. The alpha-hydroxy acid is lactic acid, tartaric acid, citric...

...tourmaline, caffeine, and/or theophylline. The pressure-sensitive adhesive has emulsifier that is pectin. The **patch** further comprises a keratolytic agent, preferably alcloxa (up to 2 wt%, preferably 0.2-2...

...The **patch** further comprises an astringent (up to 25 wt% of the formulation), preferably alum, tannic acid...

...Preferred **Patch** : The backing comprises nonwoven fabric. Upon contact with **skin** the backing retains the cosmetic formulation and the **patch** allows moisture from the **skin** to pass. The cosmetic agent is present in 0.01-4.0 (preferably 0.1...

...The **patch** has a thickness of 0.2-0.75 mm and further comprises a release liner...

...is mounted to the front side of the backing. More than one, preferably 2-20 **patches** can be mounted on the release liner.

Extension Abstract:

... A formulation for a **patch** comprised (wt%): polyacrylamine (13), glycerin (53.50), water (19.00), Vitamin A palmitate (0.25...

...Title Terms: **PATCH** ;

13/3,K/4 (Item 4 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
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014295205

WPI Acc No: 2002-115908/200216

XRAM Acc No: C02-035667

XRPX Acc No: N02-086481

Odor control system like diapers, sanitary napkins, etc., comprises  
cationic polysaccharide and odor controlling agent

Patent Assignee: PROCTER & GAMBLE CO (PROC )

Inventor: CARLUCCI G; DI CINTIO A; GAGLIARDINO A; PESCE A; GAGLIARDINI A;  
CINTIO A D

Number of Countries: 096 Number of Patents: 010

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
EP 1149595	A1	20011031	EP 2000108064	A	20000425	200216 B
WO 200180914	A1	20011101	WO 2001US13159	A	20010424	200216
AU 200157204	A	20011107	AU 200157204	A	20010424	200219
EP 1276513	A1	20030122	EP 2001930696	A	20010424	200308
			WO 2001US13159	A	20010424	
US 20030022573	A1	20030130	WO 2001US13159	A	20010424	200311
			US 2002238414	A	20020910	
BR 200110374	A	20030218	BR 200110374	A	20010424	200323
			WO 2001US13159	A	20010424	
KR 2002093067	A	20021212	KR 2002714243	A	20021024	200328
JP 2003530968	W	20031021	JP 2001578008	A	20010424	200373
			WO 2001US13159	A	20010424	
CN 1437487	A	20030820	CN 2001808604	A	20010424	200374
MX 2002009947	A1	20030201	WO 2001US13159	A	20010424	200413
			MX 20029947	A	20021008	

C-1-P OF  
PCT  
FILE  
DATE  
24 APRIL  
2001

Priority Applications (No Type Date): EP 2000108064 A 20000425

Patent Details:

Patent No Kind Lan Pg Main IPC Filing Notes

EP 1149595 A1 E 23 A61L-015/28

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI

WO 200180914 A1 E A61L-015/28

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA  
CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS  
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL  
PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR  
IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

AU 200157204 A A61L-015/28 Based on patent WO 200180914

EP 1276513 A1 E A61L-015/28 Based on patent WO 200180914

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI TR

US 20030022573 A1 B32B-027/04 Cont of application WO 2001US13159

BR 200110374 A A61L-015/28 Based on patent WO 200180914

KR 2002093067 A A61L-015/28

JP 2003530968 W 54 A61F-013/15 Based on patent WO 200180914

CN 1437487 A A61L-015/28

MX 2002009947 A1 A61L-015/28 Based on patent WO 200180914

Abstract (Basic):

... For diapers, sanitary napkins, panty liners, tampon, incontinent  
pad, breast pad, perspiration pad, human or animal waste  
management device, inter labial pad or body cleansing material  
(claimed...)



...The material is compliant and has soft feeling, without irritating the wearer's skin .

Technology Focus:

... Preferred Composition: The cationic polysaccharide is an amino polysaccharide, preferably a **chitosan** material chosen from **chitosan** , **chitosan** salt, modified **chitosan** and/or cross-linked **chitosan** .  
...

...Preferred Properties: The **chitosan** material has a degree of de-acetylation of more than 75%, preferably 95-100

Extension Abstract:

... The **chitosan** material is a **chitosan** salt of citric acid, formic acid, acetic acid, N-acetylglycine, acetylsalicylic acid, fumaric acid, glycolic acid, iminodiacetic acid, itaconic acid, lactic acid, maleic acid, malic acid, **nicotinic acid** , salicylic acid, succinamic acid , succinic acid , **ascorbic acid** , aspartic acid , glutamic acid, glutaric acid, malonic acid, pyruvic acid, sulfonyl diacetic acid, benzoic acid, epoxy succinic...

...A (0.3) as odor controlling agent, were uniformly dispersed in a commercially available feminine pad , and evaluated. The odor controlling properties against malodorous compounds associated with body fluids, were excellent.

International Patent Class (Main): A61F-013/15 ...

International Patent Class (Additional): A61F-005/441 ...

... A61F-013/00 ...

... A61F-013/20 ...

... A61F-013/472 ...

... A61F-013/49

13/3,K/5 (Item 5 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
(c) 2004 Thomson Derwent. All rts. reserv.

014295204

WPI Acc No: 2002-115907/200216

XRAM Acc No: C02-035666

XRPX Acc No: N02-086480

Article such as disposable absorbent article, sanitary napkin,  
pantiliner, tampon, diaper, incontinent pad, breast pad, perspiration  
pad, comprises chitosan material and ionic absorbent gelling material

Patent Assignee: PROCTER & GAMBLE CO (PROC )

Inventor: CARLUCCI G; DI CINTIO A; GAGLIARDINI A; PESCE A; GAGLIARDINI A J

Number of Countries: 096 Number of Patents: 013

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
EP 1149594	A1	20011031	EP 2000108063	A	20000425	200216 B
WO 200180912	A1	20011101	WO 2001US13157	A	20010424	200216
AU 200157202	A	20011107	AU 200157202	A	20010424	200219
EP 1276511	A1	20030122	EP 2001930694	A	20010424	200308
			WO 2001US13157	A	20010424	
US 20030049480	A1	20030313	WO 2001US13157	A	20010424	200321
			US 2002251071	A	20020920	
BR 200110189	A	20030305	BR 200110189	A	20010424	200322
			WO 2001US13157	A	20010424	
KR 2002093080	A	20021212	KR 2002714360	A	20021025	200328
CZ 200203511	A3	20030416	WO 2001US13157	A	20010424	200336
			CZ 20023511	A	20010424	
CN 1426315	A	20030625	CN 2001808603	A	20010424	200362
ZA 200208091	A	20030923	ZA 20028091	A	20021008	200368
HU 200300502	A1	20030929	WO 2001US13157	A	20010424	200369
			HU 2003502	A	20010424	
JP 2003530966	W	20031021	JP 2001578006	A	20010424	200373
			WO 2001US13157	A	20010424	
MX 2002009844	A1	20030301	WO 2001US13157	A	20010424	200413
			MX 20029844	A	20021004	

C-1-P  
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PCT  
FILE  
DATE  
24 APRIL  
2001

Priority Applications (No Type Date): EP 2000108063 A 20000425

Patent Details:

Patent No	Kind	Lan Pg	Main IPC	Filing Notes
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EP 1149594	A1	E	20 A61L-015/28	
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Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI

WO 200180912	A1	E	A61L-015/28	
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Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA  
CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS  
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL  
PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR  
IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

AU 200157202	A		A61L-015/28	Based on patent WO 200180912
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EP 1276511	A1	E	A61L-015/28	Based on patent WO 200180912
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Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI TR

US 20030049480	A1		B32B-023/04	Cont of application WO 2001US13157
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BR 200110189	A		A61L-015/28	Based on patent WO 200180912
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KR 2002093080	A		A61L-015/28	
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CZ 200203511	A3		A61L-015/28	Based on patent WO 200180912
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CN 1426315	A		A61L-015/28	
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ZA 200208091	A	49	A61L-000/00	
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HU 200300502	A1		A61L-015/28	Based on patent WO 200180912
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JP 2003530966 W      46 A61L-015/00      Based on patent WO 200180912  
MX 2002009844 A1      A61L-015/28      Based on patent WO 200180912

Article such as disposable absorbent article, sanitary napkin, pantiliner, tampon, diaper, incontinent pad, breast pad, perspiration pad, comprises chitosan material and ionic absorbent gelling material

Abstract (Basic):

... An article comprises a **chitosan** material and an ionic absorbent gelling material.  
... which involves contacting bodily exudates and/or bodily fluids with an odor control system comprising **chitosan** material and ionic absorbent gelling material...  
...As article such as disposable absorbent article, sanitary napkin, pantiliner, tampon, diaper, incontinent pad, breast pad, perspiration pad or interlabial pad, or body cleaning article (claimed), feminine, human or animal waste management devices. The articles designed to be placed against or in proximity to the body such as clothing, bandages, thermal pads, acne pads, cold pads, compresses, surgical pads / dressings and body cleaning articles like impregnated wipes/tissues (e.g. baby wipes, wipes for feminine...

Technology Focus:

... agents, ion exchange resin, perfumes, activated carbon and/or clay. Preferred Composition: The amount of **chitosan** material or its mixture is 0.5-500 g/m<sup>2</sup>, more preferably 4-50...  
...600 g/m<sup>2</sup>, more preferably 20-200 g/m<sup>2</sup>. The weight ratio of **chitosan** material to absorbent gelling material is 10:1-1:10, more preferably 3:1-1...  
...Preferred Properties: The **chitosan** material has a deacetylation degree of greater than 75%, preferably 95-100%. The **chitosan** material is water-soluble and is acidic having pH of 4-6...

Extension Abstract:

... The **chitosan** material is **chitosan** salt, preferably **chitosan** salt of citric acid, formic acid, acetic acid, N-acetylglutamine, acetylsalicylic acid, fumaric acid, glycolic acid, iminodiacetic acid, itaconic acid, lactic acid, maleic acid, nicotinic acid, salicylic acid, succinamic acid, succinic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, malonic acid, pyruvic acid, sulfonyldiacetic acid, benzoic acid, epoxysuccinic acid, adipic...

...Feminine pad was opened by cutting wrap around perforated cover stock at its bottom face along longitudinal...

...approximately the same thickness, along a plane which is parallel to the plane of the pad. 0.5 g of chitosonium pyrrolidone carboxylate (RTM: Kytamer PC) as **chitosan** material and 0.5 g of crosslinked sodium polyacrylate XZ 9589001 as anionic absorbent gelling...

...perforated cover stock was sealed along the cut by double sided adhesive tape. The feminine pad had excellent odor controlling property and fluid handling property when contacted with bodily fluids.

...Title Terms: PAD;

...International Patent Class (Additional): A61F-005/44 ...

... A61F-013/00 ...

... A61F-013/14 ...

... A61F-013/15 ...

... A61F-013/20 ...

... A61F-013/472 ...

... A61F-013/49 ...

... A61F-013/53

13/3,K/6 (Item 6 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
(c) 2004 Thomson Derwent. All rts. reserv.

014295203

WPI Acc No: 2002-115906/200216

XRAM Acc No: C02-035665

XRPX Acc No: N02-086479

Disposable absorbent articles such as pantliners, sanitary napkins,  
diaper, incontinent pad, human or animal waste management device,  
comprises cationic polysaccharide and acidic pH buffering material

Patent Assignee: PROCTER & GAMBLE CO (PROC )

Inventor: CARLUCCI G; DI CINTIO A; PESCE A; TORDONE A A

Number of Countries: 096 Number of Patents: 007

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
EP 1149593	A1	20011031	EP 2000108062	A	20000425	200216 B
WO 200180913	A1	20011101	WO 2001US13158	A	20010424	200216
AU 200157203	A	20011107	AU 200157203	A	20010424	200219
EP 1276512	A1	20030122	EP 2001930695	A	20010424	200308
			WO 2001US13158	A	20010424	
US 20030018312	A1	20030123	WO 2001US13158	A	20010424	200310
			US 2002238013	A	20020909	
JP 2003530967	W	20031021	JP 2001578007	A	20010424	200373
			WO 2001US13158	A	20010424	
MX 2002009905	A1	20030301	WO 2001US13158	A	20010424	200413
			MX 20029905	A	20021007	

Priority Applications (No Type Date): EP 2000108062 A 20000425

Patent Details:

Patent No Kind Lan Pg Main IPC Filing Notes

EP 1149593 A1 E 20 A61L-015/28

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI

WO 200180913 A1 E A61L-015/28

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA  
CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS  
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL  
PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR  
IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

AU 200157203 A A61L-015/28 Based on patent WO 200180913

EP 1276512 A1 E A61L-015/28 Based on patent WO 200180913

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI TR

US 20030018312 A1 C08B-037/08 Cont of application WO 2001US13158

JP 2003530967 W 45 A61F-013/00 Based on patent WO 200180913

MX 2002009905 A1 A61L-015/28 Based on patent WO 200180913

Disposable absorbent articles such as pantliners, sanitary napkins,  
diaper, incontinent pad, human or animal waste management device,  
comprises cationic polysaccharide and acidic pH buffering material

Abstract (Basic):

... fluids which involves contacting body fluids with the odor  
control system comprising cationic polysaccharide preferably chitin  
-based material and/or chitosan material and an acid pH buffering  
material having pH of 3.5-6.5...

...For sanitary napkin, pantliner, tampon, diaper, incontinent pad,

C-1-P

OF

PCT

FILE  
DATE

24  
APRIL

2001

breast pad , human or animal waste management device, perspiration pad , interlabial pad or body cleaning article (claimed). Also for surgical/ dressing pads , clothing, bandages , thermal pads , acne pads , cold pads , body cleansing articles like impregnated tissues (baby wipes, wipes for feminine intimate hygiene), articles for...

...The addition of pH buffering material resulted in improved safety and skin properties of cationic polysaccharides. Enhancing cationic properties of chitosan materials enhances binding to negatively charged surface of skin in case of rewetting occurrence, thereby moisturizing the skin and providing long lasting softness and fullness. The articles deliver improved odor control performance even ...

Technology Focus:

... Preferred Polysaccharide: The cationic polysaccharide is chitosan material selected from chitosan , chitosan salt, modified chitosan , cross-linked chitosan . The acetylation degree of chitosan material is more than 75% preferably 95-100%.

Extension Abstract:

... The chitosan salt is a salt of citric acid, formic acid, acetic acid, N-acetylglycine, acetylsalicylic acid, fumaric acid, glycolic acid, iminodiacetic acid, itaconic acid, lactic acid, maleic acid, malic acid, nicotinic acid , salicylic acid , succinic acid , ascorbic acid , aspartic acid , glutamic acid, glutaric acid, malonic acid, pyruvic acid, sulfonyl diacetic acid, benzoic acid, epoxy succinic...

...A feminine pad was opened by cutting the wrap around perforated cover stock at the bottom along longitudinal...

...which was parallel to the plane of the napkin. A wet powder prepared by mixing chitosan powder material ( chitosan pyrrolidone carboxylate and acidic pH buffering material (citric acid/sodium hydroxide solution (pH 5) at...

...around perforated cover stock was sealed along the cut using double sided adhesive tape. The pads exhibited outstanding odor control properties and fluid handling properties when contacted with bodily fluids.

...Title Terms: PAD ;

International Patent Class (Main): A61F-013/00 ...

International Patent Class (Additional): A61F-005/44 ...

... A61F-013/15 ...

... A61F-013/20 ...

... A61F-013/472

13/3,K/7 (Item 7 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
(c) 2004 Thomson Derwent. All rts. reserv.

014287046

WPI Acc No: 2002-107747/200215

XRAM Acc No: C02-033228

XRPX Acc No: N02-080219

Disposable absorbent article such as a sanitary napkin, tampon or diaper,  
with improved odor control performance and fluid absorption performance,  
comprises cationic polysaccharide and silicate

Patent Assignee: PROCTER & GAMBLE CO (PROC )

Inventor: CARLUCCI G; DI CINTIO A; PESCE A; TORDONE A A; CINTIO A D

Number of Countries: 096 Number of Patents: 007

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
EP 1149596	A1	20011031	EP 2000108065	A	20000425	200215 B
WO 200180915	A1	20011101	WO 2001US13160	A	20010424	200215
AU 200157205	A	20011107	AU 200157205	A	20010424	200219
EP 1276514	A1	20030122	EP 2001930697	A	20010424	200308
			WO 2001US13160	A	20010424	
US 20030022574	A1	20030130	WO 2001US13160	A	20010424	200311
			US 2002241891	A	20020912	
JP 2003530969	W	20031021	JP 2001578009	A	20010424	200373
			WO 2001US13160	A	20010424	
MX 2002010031	A1	20030201	WO 2001US13160	A	20010424	200413
			MX 200210031	A	20021010	

E.P.  
FILE  
DATE  
25 APRIL  
2000

Priority Applications (No Type Date): EP 2000108065 A 20000425

Patent Details:

Patent No Kind Lan Pg Main IPC Filing Notes

EP 1149596 A1 E 22 A61L-015/28

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI

WO 200180915 A1 E A61L-015/28

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA  
CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS  
JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL  
PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR  
IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

AU 200157205 A A61L-015/28 Based on patent WO 200180915

EP 1276514 A1 E A61L-015/28 Based on patent WO 200180915

Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI TR

US 20030022574 A1 B32B-027/04 Cont of application WO 2001US13160

JP 2003530969 W 51 A61F-013/15 Based on patent WO 200180915

MX 2002010031 A1 A61L-015/28 Based on patent WO 200180915

Abstract (Basic):

... the body exudates and/or body fluids, with odor control system  
comprising cationic polysaccharide, preferably chitosan material,  
together with silicate...

...2) the use of the cross-linked silicate-cationic polysaccharide, namely  
cross-linked silicate- chitosan in an absorbent article suitable to be  
placed against or in proximity to the body...

...Such as sanitary napkin, pantiliner, tampon, diaper, incontinent pad ,  
breast pad , perspiration pad , interlabial pad , and body cleaning  
article (all claimed), for absorbing body fluids including instance

perspiration, urine, menstrual...

...associated with body fluids like menses. The increased degree of deacetylation, improves cationic character of **chitosan**, thereby increasing anti-microbial property, absorbing ability and gelifying ability. The addition of anionic gelling...

Technology Focus:

... Preferred Compound: The cationic polysaccharide is an amino polysaccharide, preferably a **chitosan** material chosen from the group of **chitosan**, **chitosan** salt, modified **chitosan** and/or cross-linked **chitosan**. The **chitosan** salt is typically the **chitosan** salt of citric acid, formic acid, acetic acid, N-acetylglycine, acetylsalicylic acid, fumaric acid, glycolic acid, iminodiacetic acid, itaconic acid, lactic acid, maleic acid, malic acid, **nicotinic acid**, salicylic acid, succinamic acid, succinic acid, **ascorbic acid**, aspartic acid, glutamic acid, glutaric acid, malonic acid, pyruvic acid, sulfonyl diacetic acid, benzoic acid, epoxy succinic...

...Preferred Composition: The cationic polysaccharide is **chitosan** material having degree of deacetylation of more than 75%, preferably 95-100%. The article comprises...

Extension Abstract:

... Chitosonium pyrrolidone carboxylate (**chitosan** powder) (1 g) was mixed with citric acid (0.5 g) in distilled water (100...

...was filtered dried at 100degreesC for 5 hours to obtain a powder of cross linked **chitosan** -silicate. The cross-linked **chitosan** -silicate powder (0.5 g) was homogeneously distributed between the two fibrous layers. Then, the...

...top sheet and back sheet. The absorbent article formed using absorbent core comprising cross-linked **chitosan** -silicate, had improved odor control benefits and fluid handling benefits when coming into contact with...

International Patent Class (Main): **A61F-013/15** ...

International Patent Class (Additional): **A61F-005/441** ...

... **A61F-013/00** ...

... **A61F-013/14** ...

... **A61F-013/20** ...

... **A61F-013/472** ...

... **A61F-013/49** ...

... **A61F-013/53**



Set	Items	Description
S1	84	AU=(MALIK S? OR MALIK, S?)
S2	0	SOHAIL(2W)MALIK
S3	103651	IC=A61F?
S4	2	S1:S2 AND S3
S5	4	S1 AND (COMFEEL? OR GAUZ? OR PATCH? OR DRESSING? OR BANDAG- E? OR COMPRESS? OR BAND AID? OR BAND() (AID OR AIDS))
S6	5	S4:S5
S7	5	IDPAT (sorted in duplicate/non-duplicate order)

? show files

File 347:JAPIO Nov 1976-2004/Feb(Updated 040607)  
(c) 2004 JPO & JAPIO

File 350:Derwent WPIX 1963-2004/UD,UM &UP=200442  
(c) 2004 Thomson Derwent

7/3,K/1 (Item 1 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
(c) 2004 Thomson Derwent. All rts. reserv.

015922427 \*\*Image available\*\*  
WPI Acc No: 2004-080267/200408  
XRAM Acc No: C04-032928  
XRPX Acc No: N04-064103

THIS APPLICATION

**Adhesive bandage for treating acute wounds, burn wounds, and irritations, includes adhesive layer, absorbent layer, and wound healing antimicrobial agent and hemostatic agent**

Patent Assignee: KIMBERLY-CLARK WORLDWIDE INC (KIMB )

Inventor: MALIK S

Number of Countries: 101 Number of Patents: 003

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
US 20030125654	A1	20030703	US 200135059	A	20011228	200408 B
WO 200357265	A1	20030717	WO 2002US29813	A	20020918	200408
AU 2002327666	A1	20030724	AU 2002327666	A	20020918	200421

Priority Applications (No Type Date): US 200135059 A 20011228

Patent Details:

Patent No	Kind	Lan Pg	Main IPC	Filing Notes
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US 20030125654	A1	18	A61F-013/00	
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WO 200357265	A1 E		A61L-015/44	
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Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

AU 2002327666	A1		A61L-015/44	Based on patent WO 200357265
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**Adhesive bandage for treating acute wounds, burn wounds, and irritations, includes adhesive layer, absorbent layer, and wound...**

Inventor: MALIK S

Abstract (Basic):

... An adhesive **bandage** comprises a layer including top and bottom surfaces (75, 76), an adhesive layer (77), an...

... An adhesive **bandage** comprises a first layer for covering a wound site and an area around the wound...

...surfaces; a second adhesive layer on the first layer bottom surface, for adhering the adhesive **bandage** to a wound site; a third absorbent layer on the second layer, for absorbing exudates...

...single wound healing agent with antimicrobial and hemostatic functionality, each agent associated with the adhesive **bandage** in a position where the agent will come in contact with the wound site, and which are transferable from the adhesive **bandage** to the wound site...

...An INDEPENDENT CLAIM is also included for a method of producing an adhesive **bandage** comprising providing an adhesive **bandage**; and treating either the absorbent layer and/or the fourth layer, to include a wound...

...wound healing agent with hemostatic and antimicrobial multifunctionality, which agents are transferable from the adhesive **bandage** to the wound site...

...The figure shows an exploded view of the bandage .

...Title Terms: BANDAGE ;

International Patent Class (Main): A61F-013/00 ...

7/3,K/2 (Item 2 from file: 350)

DIALOG(R)File 350:Derwent WPIX

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015833645 \*\*Image available\*\*

WPI Acc No: 2003-895849/200382

XRPX Acc No: N03-714782

Longitudinal flexible stent for surgical system, has cylindrical segments with inner tubes, in which stent patterns aligning with stent patterns on outer tubes are formed

Patent Assignee: ADVANCED CARDIOVASCULAR SYSTEM (ADCA-N)

Inventor: HOSSAINY S F A; MALIK S M ; WU S

Number of Countries: 001 Number of Patents: 001

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
US 6641607	B1	20031104	US 2000753294	A	20001229	200382 B

Priority Applications (No Type Date): US 2000753294 A 20001229

Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 6641607	B1	17	A61F-002/06		

...Inventor: MALIK S M

International Patent Class (Main): A61F-002/06

7/3,K/3 (Item 3 from file: 350)

DIALOG(R)File 350:Derwent WPIX

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015650231 \*\*Image available\*\*

WPI Acc No: 2003-712414/200367

XRAM Acc No: C03-195789

XRPX Acc No: N03-569951

Bandage useful for acute wound, burn wound and irritation comprises first layer for covering wound site area and second layer for absorbing exudates including poly(ethyleneoxide)based and chitosan-based compound

Patent Assignee: KIMBERLY-CLARK WORLDWIDE INC (KIMB )

Inventor: MALIK S ; SOERENS D A

Number of Countries: 101 Number of Patents: 002

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200357267	A1	20030717	WO 2002US36556	A	20021112	200367 B
AU 2002352697	A1	20030724	AU 2002352697	A	20021112	200421

Priority Applications (No Type Date): US 200134906 A 20011228

Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200357267	A1	E	31	A61L-015/60	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB  
GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW  
AU 2002352697 A1 A61L-015/60 Based on patent WO 200357267

Bandage useful for acute wound, burn wound and irritation comprises  
first layer for covering wound site...  
Inventor: MALIK S ...

Abstract (Basic):

... A bandage (60) comprises...

... A bandage (60) comprises...

...and chitosan-based compound. At least one wound healing antimicrobial  
agent is associated with the bandage, such that the agent will come  
in contact with the wound site and is transferable from the bandage  
to the wound site, upon contact with the wound site...

...An INDEPENDENT CLAIM is included for the preparation of bandage  
involving coating an elastomeric base sheet with a skin-friendly  
adhesive (77), and affixing absorbent...

...The bandage is used for treating acute wounds, burn wounds and  
irritations (claimed...

...The bandage is non-occlusive, capable of on-going absorption and  
retention of fluid from a wound, even under compression, while at the  
same time releasing agents to the wound that are beneficial for  
promoting...

...The figure shows an exploded perspective view of an adhesive bandage.

... Bandage (60

Technology Focus:

... Preferred Bandage : The chitosan is between 0.01 - 75%, and the  
wound healing antimicrobial agent is between 0.1 - 70 wt.% of the  
absorbent layer. The bandage further contains an adhesive layer (77)  
between the first and second layer for adhesively bonding the bandage  
to a wound site. The wound healing antimicrobial agent is situated in  
or on the...

...which is coated with the poly(ethylene oxide)-based material or  
chitosan-based material. The bandage further comprises a third layer  
(85/90) over the second layer containing a perforated anti...

...Preferred Bandage : The absorbent layer is poly(ethyleneoxide) resin  
that is modified by grafting with an alkoxy...

Title Terms: BANDAGE ;

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7/3,K/4 (Item 4 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
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015229067

WPI Acc No: 2003-289980/200328

Related WPI Acc No: 2003-381408

XRAM Acc No: C03-075310

Novel peptide inhibitor of proteinase activity of matrix  
metalloproteinases, e.g. matrix metalloproteinase-2, useful for  
stimulating cellular proliferation of fibroblasts or keratinocytes

Patent Assignee: KIMBERLY-CLARK WORLDWIDE INC (KIMB ); MALIK S (MALI-I);  
QUIRK S (QUIR-I)

Inventor: MALIK S ; QUIRK S; VILLANUEVA J M

Number of Countries: 102 Number of Patents: 004

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200316520	A1	20030227	WO 2002US26198	A	20020815	200328 B
US 20030148959	A1	20030807	US 2001312726	P	20010816	200358
			US 200132376	A	20011221	
			US 2002153185	A	20020521	
US 20030166567	A1	20030904	US 2001312726	P	20010816	200359
			US 200132376	A	20011221	
			US 2002153185	A	20020521	
			US 2002219561	A	20020815	
EP 1423515	A1	20040602	EP 2002759388	A	20020815	200436
			WO 2002US26198	A	20020815	

Priority Applications (No Type Date): US 2002153185 A 20020521; US  
2001312726 P 20010816; US 200132376 A 20011221; US 2002219561 A 20020815

Patent Details:

Patent No	Kind	Lan Pg	Main IPC	Filing Notes
WO 200316520	A1	E 120	C12N-009/99	
Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW				
Designated States (Regional): AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW				
US 20030148959	A1		A61K-038/10	Provisional application US 2001312726
				CIP of application US 200132376
US 20030166567	A1		A61K-038/10	Provisional application US 2001312726
				CIP of application US 200132376
				CIP of application US 2002153185
EP 1423515	A1	E	C12N-009/99	Based on patent WO 200316520
Designated States (Regional): AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR				

Inventor: MALIK S ...

Abstract (Basic):

... 3) a wound dressing (II) comprising (Ia) or (Ib) which can  
inhibit matrix metalloproteinase or the peptide can stimulate...

Technology Focus:

... Preferred: The dressing promotes wound healing, prevents  
scarring, improve skin tone, reduces wrinkling, or stimulates the  
development of...

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7/3,K/5 (Item 5 from file: 350)  
DIALOG(R)File 350:Derwent WPIX  
(c) 2004 Thomson Derwent. All rts. reserv.

014806627

WPI Acc No: 2002-627333/200267

XRAM Acc No: C04-012632

Formation of coating on article such as medical instruments; bandages ,  
involves contacting article with copolymer of water-base polymer grafted  
with organic moiety having silanol forming group, and curing copolymer

Patent Assignee: KIMBERLY-CLARK WORLDWIDE INC (KIMB ); AMBROSIO A A  
(AMBR-I); GREENE S L (GREE-I); MALIK S (MALI-I); ROUNS C G (ROUN-I);  
SOERENS D (SOER-I)  
Inventor: AMBROSIO A A; GREENE S L; MALIK S ; ROUNS C G; SOERENS D A;  
SOERENS D

Number of Countries: 099 Number of Patents: 005

Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
WO 200253664	A2	20020711	WO 2001US50902	A	20011129	200267 B
US 20020132540	A1	20020919	US 2000752002	A	20001229	200269
US 6596402	B2	20030722	US 2000752002	A	20001229	200354
EP 1360254	A2	20031112	EP 2001991619	A	20011129	200377
			WO 2001US50902	A	20011129	
AU 2002231345	A1	20020716	AU 2002231345	A	20011129	200427

Priority Applications (No Type Date): US 2000752002 A 20001229

Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
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WO 200253664	A2	E	49	C09D-201/10	
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Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA  
CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN  
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ  
PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR  
IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

US 20020132540	A1			B32B-003/00	
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US 6596402	B2			B32B-009/04	
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EP 1360254	A2	E		C09D-201/10	Based on patent WO 200253664
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Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT  
LI LT LU LV MC MK NL PT RO SE SI TR

AU 2002231345	A1			C09D-201/10	Based on patent WO 200253664
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Formation of coating on article such as medical instruments, bandages ,  
involves contacting article with copolymer of water-base polymer grafted  
with organic moiety having silanol...

...Inventor: MALIK S

Abstract (Basic):

... water pipe, tube, pipeline, boat hull, submarine, torpedo,  
fishing line, fishing lure, water ski, propeller, bandages , drapes,  
fabrics (woven or nonwoven), fibers, foams, films, medical instruments  
(catheters, shunts, artificial organs, dialysis...

...Title Terms: BANDAGE ;

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Set	Items	Description
S1	62	AU=(MALIK S? OR MALIK, S?)
S2	0	SOHAIL(2W)MALIK
S3	36749	IC=A61F?
S4	0	S1:S2 AND S3
S5	11	S1 AND (COMFEEL? OR GAUZ? OR PATCH? OR DRESSING? OR BANDAG- E? OR COMPRESS? OR BAND AID? OR BAND() (AID OR AIDS))
S6	11	IDPAT (sorted in duplicate/non-duplicate order)

? show files

File 348:EUROPEAN PATENTS 1978-2004/Jun W03  
(c) 2004 European Patent Office

File 349:PCT FULLTEXT 1979-2002/UB=20040701,UT=20040624  
(c) 2004 WIPO/Univentio

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6/3,AU/1 (Item 1 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
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01627597

BANDAGE FOR ABSORBING EXUDATES COMPRISING POLY(ETHYLENEOXIDE) - AND  
CHITOSAN-BASED COMPOUNDS  
BANDAGE ZUR ABSORBIERUNG VON WUNDEXSUDAT, DIE POLYETHYLENOXID- UND  
CHITOSAN- BASIERTE VERBINDUNGEN ENTALTEND  
PANSEMENT ABSORBANT L'EXSUDAT, COMPRENANT DES COMPOSES A BASE DE  
POLY(ETHYLENEOXYDE) ET CHITOSANE

PATENT ASSIGNEE:

KIMBERLY-CLARK CORPORATION, (403966), 401 North Lake Street, Neenah,  
Wisconsin 54956, (US), (Applicant designated States: all)

INVENTOR:

SOERENS, Dave, Allen, 736 Kensington Road, Neenah, WI 54956, (US)

MALIK, Sohail , 4420 Calibre Creek Parkway, Roswell, GA 30076, (US)

PATENT (CC, No, Kind, Date):

WO 2003057267 030717

APPLICATION (CC, No, Date): EP 2002789646 021112; WO 2002US36556 021112

PRIORITY (CC, No, Date): US 34906 011228

DESIGNATED STATES: AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR;  
IE; IT; LI; LU; MC; NL; PT

EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI

INTERNATIONAL PATENT CLASS: A61L-015/60

LANGUAGE (Publication,Procedural,Application): English; English; English

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6/3,AU/2 (Item 2 from file: 349)  
DIALOG(R)File 349:PCT FULLTEXT  
(c) 2004 WIPO/Univentio. All rts. reserv.

01027585

BANDAGE FOR ABSORBING EXUDATES COMPRISING POLY(ETHYLENEOXIDE) - AND  
CHITOSAN-BASED COMPOUNDS  
PANSEMENT ABSORBANT L'EXSUDAT, COMPRENANT DES COMPOSES A BASE DE  
POLY(ETHYLENEOXYDE) ET CHITOSANE

Patent Applicant/Assignee:

KIMBERLY-CLARK WORLDWIDE INC, 401 N. Lake Street, Neenah, WI 54956, US,  
US (Residence), US (Nationality)

Inventor(s):

SOERENS Dave Allen, 736 Kensington Road, Neenah, WI 54956, US,

MALIK Sohail , 4420 Calibre Creek Parkway, Roswell, GA 30076, US

Legal Representative:

ROBINSON James B (et al) (agent), Kimberly-Clark Worldwide, Inc., 401 N.  
Lake St., Neenah, WI 54956, US,

Patent and Priority Information (Country, Number, Date):

Patent: WO 200357267 A1 20030717 (WO 0357267)

Application: WO 2002US36556 20021112 (PCT/WO US0236556)

Priority Application: US 200134906 20011228

Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU  
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP  
KR KZ LC LK LR LS LT LU MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO  
RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW  
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR  
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG  
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW  
(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English

Filing Language: English



Fulltext Word Count: 20015

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6/3,AU/3 (Item 3 from file: 348)  
DIALOG(R)File 348:EUROPEAN PATENTS  
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01627368

ADHESIVE BANDAGE CONTAINING AN ANTIMICROBIAL AND AN HEMOSTATIC AGENT  
SELBSTKLEBENDER WUNDVERBAND ENTHALTEND EIN ANTIMIKROBIELLES UND EIN  
BLUTSTILLENDESMITTEL

PANSEMENT ADHESIF CONTENANT UN AGENT ANTIMICROBIEN ET UN AGENT HEMOSTATIQUE  
PATENT ASSIGNEE:

KIMBERLY-CLARK WORLDWIDE, INC., (2258250), 401 North Lake Street, Neenah,  
Wisconsin 54956, (US), (Applicant designated States: all)

INVENTOR:

MALIK, Sohail , 4420 Calibre Creek Parkway, Roswell, GA 30076, (US  
PATENT (CC, No, Kind, Date):

WO 2003057265 030717

APPLICATION (CC, No, Date): EP 2002763667 020918; WO 2002US29813 020918

PRIORITY (CC, No, Date): US 35059 011228

DESIGNATED STATES: AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR;

IE; IT; LI; LU; MC; NL; PT

EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI

INTERNATIONAL PATENT CLASS: A61L-015/44; A61L-015/58; A61K-031/722

LANGUAGE (Publication,Procedural,Application): English; English; English

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6/3,AU/4 (Item 4 from file: 349)  
DIALOG(R)File 349:PCT FULLTEXT  
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01027584

ADHESIVE BANDAGE CONTAINING AN ANTIMICROBIAL AND AN HEMOSTATIC AGENT  
PANSEMENT ADHESIF CONTENANT UN AGENT ANTIMICROBIEN ET UN AGENT HEMOSTATIQUE  
Patent Applicant/Assignee:

KIMBERLY-CLARK WORLDWIDE INC, 401 N. Lake Street, Neenah, WI 54956, US,  
US (Residence), US (Nationality)

Inventor(s):

MALIK Sohail , 4420 Calibre Creek Parkway, Roswell, GA 30076, US  
Legal Representative:

ROBINSON James B (et al) (agent), Kimberly-Clark Worldwide, Inc., 401 N.  
Lake Street, Neenah, WI 54956, US,

Patent and Priority Information (Country, Number, Date):

Patent: WO 200357265 A1 20030717 (WO 0357265)

Application: WO 2002US29813 20020918 (PCT/WO US0229813)

Priority Application: US 200135059 20011228

Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU

CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP

KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO

RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR

(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English

Filing Language: English

Fulltext Word Count: 6817

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6/3,AU/5 (Item 5 from file: 349)  
DIALOG(R)File 349:PCT FULLTEXT  
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01130692

**COMPUTER SYSTEM PERFORMANCE ANALYSIS**  
**ANALYSE DE PERFORMANCE D'UN SYSTEME INFORMATIQUE**

Patent Applicant/Assignee:

SYSTEMS INTELLIGENCE LTD, Teknik House, Bedford Road, Tunbridge Wells,  
Kent TN11 9BS, GB, GB (Residence), GB (Nationality), (For all designated  
states except: US)

Patent Applicant/Inventor:

**MALIK Shakiel**, 32 Montagu Road, Datchet, Berkshire SL3 9DJ, GB, GB  
(Residence), GB (Nationality), (Designated only for: US)  
**HALEWOOD Keith**, 4 Sheridan Court, Tonbridge Road, Hildenborough, Kent  
TN11 9BS, GB, GB (Residence), GB (Nationality), (Designated only for:  
US

Legal Representative:

PARABOLA (agent), 1 Richfield Place, Richfield Avenue, Reading RG1 8EQ,  
GB,

Patent and Priority Information (Country, Number, Date):

Patent: WO 200453695 A1 20040624 (WO 0453695)

Application: WO 2002GB5515 20021206 (PCT/WO GB02005515)

Priority Application: WO 2002GB5515 20021206

Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU  
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP  
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO  
RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW  
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SI SK  
TR

(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English

Filing Language: English

Fulltext Word Count: 4007

*DISREGARD*

6/3,AU/6 (Item 6 from file: 349)  
DIALOG(R)File 349:PCT FULLTEXT  
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01123371

**HUMAN ACID-SENSING ION CHANNEL 2b (hASIC2b)**

**CANAL IONIQUE 2B HUMAIN DETECTEUR D'ACIDE (HASIC2B)**

Patent Applicant/Assignee:

EURO-CELTIQUE S A, 122, Boulevard de la Petrusse, L-2330 Luxembourg, LU,  
LU (Residence), LU (Nationality), (For all designated states except:  
US)

Patent Applicant/Inventor:

**KAMMESHEIDT Anja**, 31558 Eagle Rock Way, Laguna Beach, CA 92651, US, US  
(Residence), DE (Nationality), (Designated only for: US)

**MALIK Shiazah Z**, 2965 South Fairview Street, Unit D, Santa Ana, CA  
92704, US, US (Residence), GB (Nationality), (Designated only for: US

Legal Representative:

FEHLNER Paul F (et al) (agent), Darby & Darby P.C., P.O. Box 5257, New  
York, NY 10150-5257, US,

Patent and Priority Information (Country, Number, Date):

Patent: WO 200444162 A2 20040527 (WO 0444162)

Application: WO 2003US35870 20031106 (PCT/WO US03035870)

Priority Application: US 2002424496 20021106

*DISREGARD*

Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU  
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP  
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL  
PT RO RU SC SD SE SG SK SL SJ TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA  
ZM ZW  
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE  
SI SK TR  
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG  
(AP) BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW  
(EA) AM AZ BY KG KZ MD RU TJ TM  
Publication Language: English  
Filing Language: English  
Fulltext Word Count: 16543

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6/3,AU/7 (Item 7 from file: 349)  
DIALOG(R)File 349:PCT FULLTEXT  
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01067034

**CELL PROLIFERATING AGENTS**  
**AGENTS DE PROLIFERATION CELLULAIRE**

Patent Applicant/Assignee:

KIMBERLY-CLARK WORLDWIDE INC, 401 N. Lake Street, Neenah, WI 54956, US,  
US (Residence), US (Nationality)

Inventor(s):

**MALIK Sohail** , 4420 Calibre Creek Parkway, Roswell, GA 30076, US

Legal Representative:

CROSBY Margaret M (et al) (agent), PAULEY PETERSEN KINNE & ERICKSON, 2800  
West Higgins Road, Suite 365, Hoffman Estates, IL 60195, US,

Patent and Priority Information (Country, Number, Date):

Patent: WO 200394907 A1 20031120 (WO 0394907)

Application: WO 2003US6754 20030305 (PCT/WO US0306754)

Priority Application: US 2002140270 20020506

Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU  
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP  
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO  
RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE  
SI SK TR

(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English

Filing Language: English

Fulltext Word Count: 5564

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6/3,AU/8 (Item 8 from file: 349)  
DIALOG(R)File 349:PCT FULLTEXT  
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01029112

**COMPOSITIONS AND METHODS FOR INCREASING CELL PROLIFERATION COMPRISING A  
FLAVONOID**

**COMPOSITIONS ET METHODES D'AUGMENTATION DE LA PROLIFERATION CELLULAIRE  
CONTENANT UN FLAVONOIDE**

Patent Applicant/Assignee:

KIMBERLY-CLARK WORLDWIDE INC, 401 N. Lake Street, Neenah, WI 54956, US,  
US (Residence), US (Nationality)

Inventor(s):

**MALIK Sohail** , 4420 Calibre Creek Parkway, Roswell, GA 30076, US

Legal Representative:

TULLEY Douglas H Jr (et al) (agent), Kimberly-Clark Worldwide, Inc., 401 N. Lake St., Neenah, WI 54956, US,

Patent and Priority Information (Country, Number, Date):

Patent: WO 200357210 A1 20030717 (WO 0357210)

Application: WO 2002US37011 20021118 (PCT/WO US0237011)

Priority Application: US 200134150 20011229

Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU

CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP

KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO

RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR

(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English

Filing Language: English

Fulltext Word Count: 6749

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6/3,AU/9 (Item 9 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

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00988110

**ANTI-AGING AND WOUND HEALING COMPOUNDS**

**COMPOSES ANTI-AGE ET DE CICATRISATION DE PLAIES**

Patent Applicant/Assignee:

KIMBERLY-CLARK WORLDWIDE INC, 401 N. Lake Street, Neenah, WI 54956, US,  
US (Residence), US (Nationality)

Inventor(s):

QUIRK Stephen, 545 Morton Mill Court, Alpharetta, GA 30022, US,

**MALIK Sohail** , 4420 Calibre Creek Parkway, Roswell, GA 30076, US,

VILLANUEVA Julie M, 205 Mead Road, Decatur, GA 30030, US

Legal Representative:

CHADWICK Robin A (agent), Schwegman, Lundberg, Woessner, & Kluth, P.A.,  
1600 TCF Tower, 121 South Eighth Street, Minneapolis, MN 55402 (et al),  
US,

Patent and Priority Information (Country, Number, Date):

Patent: WO 200316520 A1 20030227 (WO 0316520)

Application: WO 2002US26198 20020815 (PCT/WO US0226198)

Priority Application: US 2001312726 20010816; US 200132376 20011221; US  
2002153185 20020521

Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU

CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP

KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO

RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR

(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English

Filing Language: English

Fulltext Word Count: 26376

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6/3,AU/10 (Item 10 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

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00920982

**ABSORBENT, LUBRICIOUS COATING AND ARTICLES COATED THEREWITH  
REVETEMENTS ABSORBANTS ET LUBRIFIANTS ET ARTICLES EN ETANT REVETUS**

Patent Applicant/Assignee:

KIMBERLY-CLARK WORLDWIDE INC, 401 North Lake Street, Neenah, WI 54956, US  
, US (Residence), US (Nationality)

Inventor(s):

SOERENS Dave A, 191 Brook Lane, Roswell, GA 30075, US,  
MALIK Sohail , 4420 Calibre Creed Parkway, Roswell, GA 30076, US,  
ROUNS Cameron G, 10136 S. Bolton, South Jordan, UT 84095, US,  
GREENE Sharon L, 235 Della Smith Lane, Canton, GA 30115, US,  
AMBROSIO Archel A, 7689 Palmilla Drive, #1302, San Diego, CA 92122, US

Legal Representative:

NELSON MULLINS RILEY & SCAROBOROUGH (agent), 1330 Lady Street, Keenan  
Building, Third Floor, Columbia, SC 29201, US,

Patent and Priority Information (Country, Number, Date):

Patent: WO 200253664 A2-A3 20020711 (WO 0253664)  
Application: WO 2001US50902 20011129 (PCT/WO US0150902)  
Priority Application: US 2000752002 20001229

Designated States: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU  
CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP  
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU  
SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW  
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR  
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG  
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW  
(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English

Filing Language: English

Fulltext Word Count: 13080

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6/3,AU/11 (Item 11 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

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00261630

**MIXTURES OR COMPLEXES CONTAINING CALCIUM AND SULFATE  
MELANGES OU COMPLEXES CONTENANT DU CALCIUM ET DU SULFATE**

Patent Applicant/Assignee:

THE BONAPARTE COMPANY,

Inventor(s):

HART Ralph M,  
JONES Herman L,  
EGELKROUT Veronica Lee,  
MALIK Sohail ,  
KENNY Margaret A,  
LOEV Bernard,  
HARNISCH James P

Patent and Priority Information (Country, Number, Date):

Patent: WO 9409798 A1 19940511  
Application: WO 93US10489 19931028 (PCT/WO US9310489)  
Priority Application: US 92969793 19921029

Designated States: AT AU BB BG BR BY CA CH CZ DE DK ES FI GB HU JP KP KR KZ  
LK LU LV MG MN MW NL NO NZ PL PT RO RU SD SE SK UA UZ AT BE CH DE DK ES  
FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

Publication Language: English

Fulltext Word Count: 9643

Set	Items	Description
S1	5656	AU=(MALIK S? OR MALIK, S?)
S2	0	SOHAIL(2W)MALIK
S3	1	IC=A61F?
S4	0	S1:S2 AND S3
S5	22	S1 AND (COMFEEL? OR GAUZ? OR PATCH? OR DRESSING? OR BANDAG- E? OR COMPRESS? OR BAND AID? OR BAND() (AID OR AIDS))

S6 15 RD (unique items)

? show files

File 2:INSPEC 1969-2004/Jun W4  
(c) 2004 Institution of Electrical Engineers

File 5:Biosis Previews(R) 1969-2004/Jun W4  
(c) 2004 BIOSIS

File 6:NTIS 1964-2004/Jun W4  
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(c) 2004 Elsevier Eng. Info. Inc.

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(c) 2004 Japan Science and Tech Corp(JST)

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File 99:Wilson Appl. Sci & Tech Abs 1983-2004/Jun  
(c) 2004 The HW Wilson Co.

File 144:Pascal 1973-2004/Jun W4  
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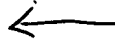
File 155:MEDLINE(R) 1966-2004/Jun W2  
(c) format only 2004 The Dialog Corp.

File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec  
(c) 1998 Inst for Sci Info

File 481:DELPHEs Eur Bus 95-2004/Jun W3  
(c) 2004 ACFCI & Chambre CommInd Paris

File 583:Gale Group Globalbase(TM) 1986-2002/Dec 13  
(c) 2002 The Gale Group

?



SIGNIFICANT

HITS

AFTER

REVIEW

Set	Items	Description
S1	35	AU=(MALIK S? OR MALIK, S?)
S2	45	SOHAIL(2W)MALIK
S3	0	IC=A61F?
S4	0	S1:S2 AND S3
S5	0	S1 AND (COMFEEL? OR GAUZ? OR PATCH? OR DRESSING? OR BANDAG- E? OR COMPRESS? OR BAND Aid? OR BAND() (AID OR AIDS))
S6	2	S2 AND (COMFEEL? OR GAUZ? OR PATCH? OR DRESSING? OR BANDAG- E? OR COMPRESS? OR BAND Aid? OR BAND() (AID OR AIDS))
S7	1	RD (unique items)

? show files

File 15:ABI/Inform(R) 1971-2004/Jun 27  
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File 16:Gale Group PROMT(R) 1990-2004/Jul 05  
(c) 2004 The Gale Group

File 47:Gale Group Magazine DB(TM) 1959-2004/Jul 01  
(c) 2004 The Gale group

File 98:General Sci Abs/Full-Text 1984-2004/Jun  
(c) 2004 The HW Wilson Co.

File 129:PHIND(Archival) 1980-2004/Jun W4  
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File 441:ESPICOM Pharm&Med DEVICE NEWS 2004/Jun W4  
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File 444:New England Journal of Med. 1985-2004/Jul W1  
(c) 2004 Mass. Med. Soc.

File 621:Gale Group New Prod.Annou.(R) 1985-2004/Jul 02  
(c) 2004 The Gale Group

*Q SIGNIFICANT HITS*

*RETER.*

*RWISW*

Set	Items	Description
S1	325437	BANDAG? OR GAUZ? OR COMFEEL? OR PATCH? OR DRESSING? OR COM-PRESS?? OR BAND Aid? OR BAND() (AID OR AIDS) OR PAD OR PADS
S2	320089	MAIM? OR SCRATCH? OR SCRAP? OR ABRASION? OR TRAUMA? OR INJ-UR? OR WOUND? OR LACERAT? OR BURN? OR IRRITATION?
S3	17027	CHITOSAN? OR C8H13NO5 OR "1398-61-4" OR 1398()61()4 OR CHI-TIN OR CHITINDEACETYLAT? OR GLUCOSAMINE(3N)POLYSACCHARID? OR -ACHITIN OR ACETYL?(2N)GLUCOSAMIN?
S4	31115	(ASCORBAT? OR ASCORBIC?) (2N) (SALT? OR ACID? OR SODIUM? OR -MINERAL? OR CALCIUM? OR MANGANES? OR MAGNESIUM?) OR VITAMINC -OR VITAMIN()C OR C6H8O6 OR "50-81-7" OR 50()81()7
S5	17665	NIACINAMID? OR NIACIN? OR NICOTINIC()ACID? OR NICOTINAMID? OR C6H5N2O OR C6H6N2O OR "98-92-0" OR 98()92()0 OR "59-67-6" -OR 59()67()6 OR (PYREDENE? OR PYRIDINE?) (2N) (CARBOXYLIC? OR C-ARBOXAMID?) OR VITAMINB3 OR VITAMIN() (B3 OR B()3)
S6	299069	HEAL? OR CURE?? OR CURING OR SKIN? OR DERMA? OR DERMI? OR -DERME? OR DERMO?
S7	36749	IC=A61F?
S8	144925	S1 AND (S2 OR S6 OR S7)
S9	325437	S8 OR S1
S10	784	S9 AND S3 AND S4 AND S5
S11	390	S10 AND S6(10N)S2
S12	12	S11 AND (S3:S5) (5N)S1
S13	17	S11 AND S3:S5(10N)S1
S14	17	S12:S13
S15	17	IDPAT (sorted in duplicate/non-duplicate order)

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**ABSORBENT ARTICLES WITH POLYSACCHARIDE-COMPRISING WINGS**  
**ARTICLES ABSORBANTS EQUIPES D'AILETTES CONTENANT UN POLYSACCHARIDE**

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Detailed Description

Claims

English Abstract

...by having side panels, so-called wings, which comprise a gel-forming  
polysaccharide, preferably a **chitosan** material.

French Abstract

...laterales, denommees ailettes, qui contiennent un polysaccharide  
formant un gel, de preference un materiau en **chitosane**.

Detailed Description

... by having side panels, so-called wings, which comprise a gel-forming  
polysaccharide, preferably a **chitosan** material.

Background of the Invention

An increasingly important consumer need, which underlies development in  
the...significant improvements in both above areas by the incorporation  
of gel-forming polysaccharides, in particular **chitosan** materials, into  
the wings. Advantageously, both problems are overcome by the use of the  
same ingredient.

Background art of the invention

EP  
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8 OCT  
2001

Articles comprising **chitosan** materials are known from the art. For example, W099/32697 discloses that **chitosan** and **chitin** -based ...when coated onto the surface of a hydrophobic material such as polypropylene. The use of **chitosan** as absorbent material for use in absorbent core structures of absorbent articles is suggested in...2 having side panels, so-called wings, which comprise a gel-forming polysaccharide, preferably a **chitosan** material.

#### Detailed Description of the Invention

The term 'longitudinal' as used herein refers to the direction of the central longitudinal axis of the central absorbent **pad** of the absorbent article of the present invention. The term 'transverse' as used herein refers...

...the transverse axis, which is generally perpendicular to the longitudinal axis, of the central absorbent **pad** of the absorbent article of the present invention.

...or retain body fluids. The absorbent article of the present invention comprises a central absorbent **pad** having a longitudinal axis and a transverse axis, longitudinal edges extending in a generally longitudinal direction and transverse ends extending in a generally transverse direction. The central absorbent **pad** of the absorbent article, which is referred to in the present invention, typically comprises a...articles according to the present invention are disposable absorbent articles for feminine protection like incontinence **pads**, sanitary napkins or panty liners.

The term 'disposable' is used herein ...to about 100% of the surface of the wings, which is facing the wearer's **skin** in the in-use folded configuration. This means in particular that the **chitosan** material is preferably located on and around the folding axis, which is generated when the...extensions of one, some or all of the materials used to provide the central absorbent **pad**.

Alternatively, the wings can be constructed separately from the absorbent central **pad**. In this case they can be made from the same materials used already for the absorbent **pad** or from different materials such as those mentioned herein

already. If provided separately, the wings are attached to the central absorbent **pad** by any means conventionally used in combining absorbent articles, such as adhesives, thermo or mechanical...The wings can extend along a small or a long portion of the central absorbent **pad**. It is preferred that the wings be as long ...or nonwoven structures, which are compliant, soft feeling and non-irritating to the wearer's **skin**. However, when wings are

incorporated into the article, the topsheet material is not only in a substantially static contact with the wearer's **skin**, as it is the case for the topsheet itself. At the same time, in case...

...the wings, said topsheet material is also in a dynamic contact with the wearer's **skin**, because when the wearer e.g. walks, the inner side of the wearer's thighs...s thighs, which can lead to increased sensitiveness on the epidermis of the wearer's **skin**.

Another negative associated with commercially available absorbent articles with wings is so-called run-off polysaccharide preferably on the **skin** -contacting surface of the wings. The gel-forming polysaccharides for use in the present invention...

...gel layer is generated on the contact surfaces of the wings with the wearer's skin. Thus, a skin contact surface with significantly lower friction between the wing's surface and the skin is generated, which results in improved skin compatibility and reduced instances of skin irritations and rash. On the other hand, run- ...crotch region, where those wings are usually extending from the longitudinal edge of the central pad of the absorbent article for attachment onto the user's undergarment according to the present...arabicum, gellan gum, scleroglucan, xanthan, K-carrageenan, glucomannan, sodium alginate, propylene glycol alginate, carboxymethyl cellulose, chitin and chitosan materials like chitosan, modified chitosan, crosslinked chitosan and chitosan salts.

Chitosan materials are preferred herein as they ...of the absorbed fluid.

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The above benefits are obtained due to the properties of chitosan material to instantaneously gelify bodily fluids encountering it. The gelification rate of chitosan material is only a few seconds towards bodily fluids, i.e., physiological fluids like menses. Without wishing to be bound by any theory, it is believed that chitosan materials ... provide fluid absorption/gelification by multiple mechanisms.

Firstly, the fluid absorption and retention characteristics of chitosan materials due to the presence in the polymer structure of ionisable cationic functional groups.

These...the limits of molecular tension are reached.

Secondly, the positively charged cationic groups of the chitosan materials will interact with negatively charged anionic group-bearing molecules present in bodily fluids, likethe use of chitosan material is compatible with skin safety.

Indeed, the cationic properties of chitosan materials allow binding to the negatively charged surface of the skin, typically in the case of perspiration occurrence thereby moisturizing the skin and providing a long lasting softness and fullness.

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Another advantage of chitosan materials in the context of the present invention is their antimicrobial activity. Thanks to this, microbes are hindered to grow in regions with high potential of skin irritations and rash.

#### Chitosan materials

By 'chitosan material' it is meant herein chitosans, modified chitosans, crosslinked chitosans, chitosan salts and any suitable mixture thereof.

Chitosan is a partially or fully deacetylated form of chitin, a naturally occurring polysaccharide. Indeed, chitosan is an aminopolysaccharide usually prepared by deacetylation of chitin (poly-beta(1 4)-N- acetyl -D- glucosamine ).

The chitosan used herein is suitably in relatively pure form. Methods for the manufacture of pure chitosan are well known. Generally, chitin is milled into a powder and dematerialized with an organic acid such as acetic acid...

...lipids are then removed by treatment with a base, such as sodium hydroxide, followed by chitin deacetylation by treatment with concentrated base, such as 40 percent sodium hydroxide. The chitosan formed is washed with water until the desired pH is reached.

Preferred chitosan materials for use herein have an average degree of deacetylation (D.A.) of more than...

...deacetylation can be determined by titration, dye adsorption, UV-VIS, IR, and NIVIR spectroscopy.

Suitable chitosan materials to use herein include both water-soluble and water insoluble chitosan. As used herein, a material will be considered to be watersoluble when it substantially dissolves...

...losing its initially particulate form and becoming essentially molecularly dispersed throughout the water solution. Preferred chitosan materials for use herein are water soluble, i.e., at least 0.5 gram, preferably at least 1 gram and more preferably at least 2 grams of the chitosan materials are soluble in 100 grams of water at 25°C and one atmosphere. By...25°C and one atmosphere in absence of precipitate.

As a general rule, the water-soluble chitosan materials will be free from a substantial degree of crosslinking, as crosslinking tends to render the chitosan materials water insoluble.

Water-soluble chitosan materials as defined herein are preferred as they have the benefit to be more active in terms of gelifying the bodily fluid. Indeed such water-soluble chitosan materials have the ability to absorb and/or electrostatically interfere with water molecules.

Chitosan materials (i.e., chitosan and - chitosan salts, modified chitosans and cross-linked chitosans) may generally have a wide range of molecular weights.

Chitosan materials with a wide range of molecular weights are suitable for use in the present invention, typically chitosan materials for use herein have a molecular weight ranging from 1000 to 10...

...weight means weight average molecular weight. Methods for determining the weight average molecular weight of chitosan materials are known to those skilled in the art.

Typical methods include for example light...gel permeation chromatography. It is generally most convenient to express the molecular weight of a chitosan material in terms of its viscosity in a 1.0 weight percent aqueous solution at 25°C with a Brookfield viscometer. It is common to indirectly measure the viscosity of the chitosan material by measuring the viscosity of a corresponding chitosan salt, such as by using a 1.0 weight percent acetic acid aqueous solution. Chitosan materials suitable for use in the present

10 invention will suitably have a viscosity in...mPa. s (100 centipoise) to about 500 mPa. s (500 centipoise).

The pH of chitosan materials depends on the preparation of the chitosan materials. Preferred chitosan materials for use herein have an acidic pH, typically in the range of 4 to...4.5 to 5. Highly preferred pH is around pH 5, which corresponds to the skin pH. By 'pH of chitosan

material' it is meant herein the pH of a 1 % **chitosan** solution (1 gram of **chitosan** material dissolved in 100 grams of distilled water) measured by pH-meter.

**Chitosan** materials with acidic pH are preferred herein as the cationic character of acidic **chitosan** materials will be increased and thus their fluid absorbing ability and gelifying ability. However too high acidity is detrimental to **skin** safety. Thus it is highly preferred herein to use **chitosan** materials with a pH in the range of 4.5 to 5.5, thereby delivering the best compromise between fluid handling/gelifying properties on one side and **skin** compatibility on the other side.

Particularly suitable **chitosan** materials for use herein are **chitosan** salts, especially water-soluble **chitosan** salts. A variety of acids can be used for forming **chitosan** salts. Suitable acids for use are soluble in water or partially soluble in water, are sufficiently acidic to form the ammonium salt of **chitosan** and yet not sufficiently acidic to cause hydrolysis of **chitosan**, and are present in amount sufficient to protonate the reactive sites of **chitosan**.

Preferred acids can be represented by the formula.

$R-(COOH)_n$

1 1

wherein n...acid, fumaric acid, glycolic acid, iminodiacetic acid, itaconic acid, lactic acid, maleic acid, malic acid, **nicotinic acid**, 2-pyrrolidone carboxylic acid, salicylic acid, succinamic acid, succinic acid, **ascorbic acid**, aspartic acid, glutamic acid, glutaric acid, malonic acid, pyruvic acid, sulfonyldiacetic acid, benzoic acid, epoxysuccinic acid, adipic acid, thiodiacetic acid and thioglycolic acid. Any **chitosan** salts formed from the reaction of **chitosan** with any of these acids are suitable for use herein.

Examples of **chitosan** salts formed with an inorganic acid include, but are not limited to, **chitosan** hydrochloride, **chitosan** hydrobromide, **chitosan** phosphate, **chitosan** sulphonate, **chitosan** chlorosulphonate, **chitosan** chloroacetate and mixtures thereof. Examples of **chitosan** salts formed with an organic acid include, but are not limited to, **chitosan** formate, **chitosan** acetate, **chitosan** lactate, **chitosan** glycolate, **chitosan** malonate, **chitosan** epoxysuccinate, **chitosan** benzoate, **chitosan** adipate, **chitosan** citrate, **chitosan** salicylate, **chitosan** propionate, **chitosan** nitrilotriacetate, **chitosan** itaconate, **chitosan**

hydroxyacetate, **chitosan** butyrate, **chitosan** isobutyrate, **chitosan** acrylate, and mixtures thereof. It is also suitable to form a **chitosan** salt using a mixture of acids including, for example, both inorganic and organic acids.

Highly preferred **chitosan** salts for use herein are those formed by the reaction of **chitosan** with an amino acid. Amino acids are molecules containing both an acidic and amino functional...

...The use of amino acids instead of other acids

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is highly preferred as those **chitosan** amino salts have higher **skin** compatibility.

Indeed most of the amino acids are naturally present on the **skin**.

Chitosan salts of pyrrolidone carboxylic acid are effective moisturizing agents and are nonirritating to skin .

Amino acids for use herein include both linear and/or cyclo amino acids.

Examples of...one as per following formula.

H<sub>2</sub>C @@ CH<sub>2</sub>

C C

O ZC

OH

H

Highly preferred chitosan salts are chitosan pyroglutarnate salt, which is a mixture of chitosan (a macromolecule) and pyroglutamic acid (independent monomers), chitosonium pyrrolidone carboxylate, which is the chitosan salt of 2 pyrrolidone carboxylic acid. Reference is made to WO 98/07618, which describes in details processes for the preparation of such chitosan salts.

Other chitosan materials suitable for use herein include cross-linked chitosans and modified chitosans . Crosslinking agents suitable for use in the present invention are generally water-soluble and do not substantially reduce the gelforming and antimicrobial properties of chitosan . One suitable crosslinking agent is an organic compound having at least two functional groups or functionalities capable of reacting with active groups located on the chitosan materials.

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Examples of such active groups include, but are not limited to, carboxylic acid...polycarboxylic acids, polyoxides and the like. One way to introduce a crosslinking agent with the chitosan solution is to mix the crosslinking agent with chitosan during preparation of the solution. Another suitable crosslinking agent comprises a metal ion with more...

...Fe 3+

3+ 4+ 3+

Ce , Ce , Ti'+, Zr@+, and Cr . Since the cations of chitosan possess antimicrobial properties, it is preferred herein to not use a crosslinking agent reacting to...is from 0.001 to 30 weight percent based on the total dry weight of chitosan used to prepare the crosslinked-chitosan , more specifically from 0.02 to 20 weight percent, more specifically from 0.05 to 1 0 weight percent and most preferably from 0.1 to 5 weight percent.

Modified chitosans for use herein are any chitosan where the glucan chains carry pendant groups. Examples of such modified chitosans include carboxymethyl chitosan , methyl pyrrolidinone chitosan , glycol chitosan and the like. Methyl pyrrolidone chitosan is for instance described in US 5 378 472. Water-soluble glycol chitosan and carboxymethyl chitosan are for instance described in Particularly suitable modified chitosans for use herein include water-soluble covalently bonded chitosan derivatives or ionically bonded chitosan derivatives obtained by contacting salt of chitosan with electrophilic organic reagents.

Reference is made to EP-A-737 692, where such water-soluble chitosan derivatives are described.

Suitable **chitosans** are commercially available from numerous vendors.

Exemplary of a commercially available **chitosan** materials are those available

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from for example the Vanson Company. The preferred **chitosan** salt for use

herein is **chitosan** pyrrolidone carboxylate (also called chitosonium pyrrolidone carboxylate), which has a degree of deacetylation of more...

...and one

atmosphere), a pH of 4.5 and a viscosity between 100-300 cps. **Chitosan** pyrrolidone carboxylate is commercially available under the name Kytamero PC from Amerchol Corporation.

Typically, the wings of the absorbent articles comprise gel-forming polysaccharide, preferably **chitosan** material, or a mixture thereof at a level of from 0.5 g/M<sup>2</sup> to...g/M<sup>2</sup> to 30 g/M<sup>2</sup>. In a preferred embodiment, the gel-forming polysaccharide, preferably **chitosan** material, or mixture thereof covers from 20 to 100% of the in-use skin-facing surface of the wings at a loading of from 0.5 g/M<sup>2</sup> to **Chitosan** materials have the ability of instantaneously changing the physical properties of bodily fluids. Indeed a gelification of the bodily fluid is obtained when the fluid comes into contact with **chitosan** material. **Chitosan** material has the advantage of having a high gelification rate. This can be quantified by...10 g/M<sup>2</sup> to 100 g/M<sup>2</sup>.

Adding anionic absorbent gelling material to the **chitosan** material is able to

further enhance the advantages of the present invention. Indeed anionic absorbent gelling materials are believed to further enhance the cationic properties of **chitosan** materials. Without to be bound by any theory, it is believed that the negatively charged anionic groups of anionic absorbent gelling materials protonate the cationic groups of **chitosan** materials, thereby enhancing their cationic properties. This translates in improved gelification properties, especially further enhanced...

...described herein (typically having a degree of neutralization of from 25% to 90%) together with **chitosan** materials in the wings of an absorbent article results in outstanding fluid absorption capacity not...

...be due to the reduction of the salt poisoning effect associated to the presence of **chitosan** materials beside ...described herein (typically having a degree of neutralization of from 25% to 90%) together with **chitosan** materials exhibits high gel strength during fluid absorption.

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In a preferred embodiment of the present invention, the **chitosan** material and the anionic absorbent gelling material are present in the wings of the absorbent article at a weight ratio of **chitosan** material to absorbent gelling material of from 10:1 to 1:10, preferably... handling is obtained.

The absorbent article

Preferred absorbent articles herein are pantliners, sanitary napkins, incontinent pads and the like. The gel-forming polysaccharide, preferably **chitosan** material (and optional absorbent gelling material), may be incorporated into the wings at any locations and preferably into the in-use skin-facing surface of the wings of such articles by any of the methods known for polysaccharide is exclusively situated on the

in-use skin -facing surface of the wings.

The chitosan material as described herein may be incorporated in particle form as a powder or granulate. When used in particle form the chitosan materials as described herein and the optional absorbent gelling material may be granulated separately and then mixed together or granulated together.

The chitosan material might also be applied onto the surface of the wings, which is facing the wearer's skin in the in-use folded configuration of the wings, by simply spraying a solution containing chitosan material and letting said layer ...to dry.

Preferably, at least a portion of the garment-facing side of the central pad of the absorbent article of the present invention is coated with a panty-fastening adhesive. This adhesive is intended to attach the central absorbent pad onto the crotch portion of the wearer's undergarment during use of this article. Any...

...adhesives being preferred. The adhesive-coated portion of the garment-facing side of the central pad is preferably covered by a suitable release liner.

#### Examples

To illustrate ...starting from an absorbent article with wings, commercially available under the name Always®. A clear chitosan solution was prepared by dissolving 1 g of chitosonium pyrrolidone carboxylate, commercially available from Amerchol...

...were sprayed onto the whole surface of each wing, which is facing the wearer's skin in the folded in-use configuration.

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#### Claim

Absorbent article suitable for feminine protection comprising a central absorbent pad having a body-facing side and a garment-facing side, a longitudinal axis and a...

...direction, and said article comprises wings extending from said longitudinal edges of said central absorbent pad, said article being characterized in that said wings comprise a gel-forming polysaccharide or a further having a surface, which faces the skin of the wearer in the in-use folded configuration, characterized in that said wings comprise a gel-forming polysaccharide or mixture thereof on said surface, which faces the skin of the wearer in the inuse folded configuration.

3 Absorbent article according to any of...

...arabicum, gellan gum, scleroglucan, xanthan, K-carrageenan, glucomannan, sodium alginate, propylene glycol alginate, carboxymethyl cellulose, chitin, and chitosan materials like

chitosan, modified chitosan, cross-linked chitosan and/or a chitosan salt and mixtures thereof, preferably said gel-forming polysaccharide is a chitosan material or mixture thereof.

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. Absorbent article according to any of the preceding claims, wherein said gel-forming polysaccharide is a **chitosan** salt or a mixture thereof and more preferably chitosonium pyrrolidone carboxylate and/or chitosonium lactate...

...said gel-forming polysaccharide is provided onto said surface of said wings, which faces the **skin** of the wearer in the in-use folded configuration, in particle form.

6 Absorbent article...1-4, characterized in that an aqueous solution of said gel-forming polysaccharide, preferably a **chitosan** material, or mixture thereof is sprayed onto said surface of said wings, which faces the **skin** of the wearer in the in-use folded configuration.

7 Absorbent article according to any...polysaccharide or mixture thereof is present on said surface of said wings, which faces the **skin** of the wearer in the in-use folded configuration of said wings at a loading...

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BREAST PADS

COMPRESSES D'ALLAITEMENT

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BREAST PADS

COMPRESSES D'ALLAITEMENT

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Detailed Description

Claims

English Abstract

The present invention relates to disposable thin breathable breast pads having a wearer facing surface and a garment facing surface, said breast pad having a water vapour permeability of more than 100 (g)/(m<sup>2</sup>/24hrs) and a stiffness of less than 600 grams. These breast pads are able to closely conform to the various anatomical shapes of the breasts of women while offering enhanced comfort and low degree of wearing awareness. The breast pad has a water vapor permeable basksheet comprising a film and a support layer, and having...

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15 OCT 2001;

EP

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16 OCT 2000

In the preferred embodiment of the present invention the breast pad according to the present invention comprises a topsheet, a backsheet and an ...storage layer). The presence of such an absorbent core has the advantage of providing breast pads being thin (less than 5 mm) with enhanced conformability (defined herein by stiffness of less...

...and enhanced integrity (defined herein by core tensile strength under wet conditions), i.e., breast pads combining at the same time the consumers noticeable advantages of discretion in use, comfort and...  
...or granular materials lost that might otherwise typically arise through apertured topsheet of the breast pads of the art is avoided. Also the use of such non-granular (fibrous) super absorbent...

...as a result of thermal bonding, reinforcing scrim is usually not required for the breast pads according to the present invention.

Other components which can be included in the absorbent core...

...a structure which under external forces such as those occurring during use of a breast pad extends in the direction of the forces or in the direction of a component of...

...3 mm,

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preferably less than 2 mm is desirable such that the resulting breast pads have a thickness of less than 5.

Tqa&haeA

The topsheet if present is compliant, soft feeling, and non-irritating to the wearer's skin. The topsheet also can have elastic characteristics allowing it to stretch in one or two...

...At least in the region where fluid is expected to be discharged onto the breast pad the apertured formed films are preferred because they are pervious to milk discharge/fluid and skin. Thus, the surface of the formed film that is in contact with the breast's skin remains dry, thereby reducing skin soiling and creating a more comfortable feel for the wearer. Suitable formed films are described...

...the high loft non-woven mentioned above or other non-woven which does provide particularly skin friendliness. Such topsheets have been disclosed for pantliners in EP-A-523 683, EP-A...

...233, or EP-A-766 953 and are applicable in a circular design to breast pads needs.

Topsheets having not a homogeneous distribution of liquid passage ways but only a portion...

...fluid absorbed and contained in the absorbent core from wetting articles that contact the breast pad such as bra/undergarments. Preferably the backsheet is impervious to liquids (e.g., milk discharge ...

...to stretch in one or two directions or even preferably in all directions,  
The breast pads according to the present invention have a breathable backsheet which is water vapor permeable, i...

...structure comprising 2 hydrophilic

thermoplastic film

In a preferred embodiment herein the breast pads have a backsheet made of a

water vapor permeable liquid impervious composite structure comprising a ...typically the support layer and typically another layer for example the core of the breast pad, the thermoplastic film having two opposing surface one facing the directly the core of the breast pad and one facing the support layer). In another embodiment of the present invention

...gelling materials with the above described composite structure (used as preferred backsheet of the breast pads herein) further contributes to the integrity of such composite structure with reduced risk of rupture

...

...granular super absorbent gelling materials.

b. Other hydrophobic/hydrophilic

In another embodiment herein the breast pads are also air permeable. Typically the breast pads herein might have an air permeability (as measured by the air permeability test method described...

...air permeability might be desirable in order to further improve the comfort benefit of breast pads herein.

Suitable backsheets for use herein to deliver air permeability are breathable backsheets comprising apertures...layers. Depending on the circumstances of the ultimate use and manufacturing of the breathable breast pad, fibres of polyethylene, polypropylene, polyester, polyacetate or combinations thereof (intra- and inter-fibres combinations) have...

...have the one with the higher fiber thickness on the outer surface of the breast pad.

In an alternative embodiment of the present invention the breathable backsheet comprises a hydrophobic, gas...

...embodiment herein a dual or multiple layer breathable backsheet composite is used in the breast pad. According to the present invention suitable breathable backsheets for use herein comprise at least a...

...second layer provides water vapor and air permeability so as to support breathability of the pad.

Such a first layer is preferably in direct contact with the absorbent core. It provides...end of the second opening of the capillary with the absorbent core in the breast pad (in contrast this may be desirable for apertured film topsheets where such loose elements provide...

...side on them such that liquid transport through the capillaries towards the outside of the pad becomes nearly impossible.

Hence these three-dimensional formed film layers are highly preferable in the context of breathable breast pads and in particular so with the additional second outer layer which is provided as hereinafter...

...g/m<sup>2</sup> and preferably less than 40.

Using as the breathable backsheet in the breast pad of the present invention, a backsheet comprising at least one breathable layer of a resilient...

...This reduction of basis weight also provides an improved material consumption structure of the whole pad .

Micro-porous backsheets may suffer from the use of particles, especially large particle size materials...

...such as can be created by particles. Therefore, the use of particles in the breast pads using a micro-porous, water vapor permeable, breathable backsheet film could create discomfort due to the closeness of wearing such breast pads . Also, any particle pressing against the micro-porous backsheet may create a local aperture which...

...the Mitsui Company, Japan.

#### Optional ingredients

Other components which can be included in the breast pad herein includes chitin and/or chitosan materials. By 'chitosan material' it is meant herein chitosans , modified chitosans , crosslinked chitosans and chitosan salts. Chitosan materials are available in powder form and fibrous form. Preferably for use herein chitosan material is used in fibrous form when added within the absorbent core. Chitosan materials might also be used herein in any location of the breast pad for example within the topsheet and/or between the topsheet and the absorbent core and/or between the absorbent core and backsheet.

Chitosan materials have been found to be particularly suitable for breast pads as an effective material for controlling milk/lactational fluid discharges (including absorbing and retaining such fluid discharges typically by gelifying it within the pad ). The use of chitosan materials in breast pads provides effective fluid absorption towards ...tendency to interfere with conventional gelling absorbent materials like polyacrylates. Also the antimicrobial activity of chitosan material prevents the formation of skin irritation or even breast infection while being safe to babies. Finally the odour control properties of chitosan materials control odour associated with such lactational fluids.

Advantageously the presence of a chitosan material (preferably a chitosan salt like chitosonium pyrrolidone carboxylate), in a breathable breast pad according to the present invention provides not only initial comfort but maintain a higher level

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of comfort during use while providing at the same time high level of protection.

Chitosan materials have the ability to instantaneously reduce fluid diffusion once they are contacted with fluids...

...absorbed fluid (e.g., reduced surface area of the stains of milk discharge in the pads ). In other words the presence of a chitosan material in a breathable pad will result in larger area of dry pad which is not soiled by fluids. Advantageously the concentration of the fluid at limited locations on the pad will maintain the overall breathability of the pad at higher level in comparison to the same pad subjected to the same amount of fluid but wherein the fluid is left to diffuse...

...to be bound by any theory, this benefit is obtained due to the properties of chitosan material to instantaneously gelify lactational fluids coming into contact with it. The gelification rate of chitosan

material is only a few seconds towards such fluids, i.e., organic fluids. The positively charged cationic groups of the **chitosan** materials will interact with negatively charged anionic functionalities present in fluids, like the carboxylic groups...

...acid). This will result in the formation of tridimensional net between cationic function of the **chitosan** materials and such molecules with anionic groups. This rapid physical change of the milk fluid will instantaneously immobilize it in the **pad** avoiding fluid transfer.

**Chitosan** is a partially or fully deacetylated form of **chitin**, a naturally occurring polysaccharide. Indeed, **chitosan** is an aminopolysaccharide usually prepared by deacetylation of **chitin** (poly-beta(1,4)-N- **acetyl** -D- **glucosamine** ).

**Chitin** occurs widely in nature, for example, in the cell walls of fungi and the hard...

...from shrimp-, lobster, and crab seafood industries typically contains about 10 to about 15 percent **chitin** and is a readily available source of supply. In the natural state, **chitin** generally occurs only in small flakes or short fibrous material, such as from the carapace...

...forms useful shaped articles without solution and re-precipitation or re-naturing.

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More specifically, **chitin** is a mucopolysaccharide, poly-N- **acetyl** -D- **glucosamine** with the following formula.

CH,OH

O-

NHCOCH<sub>3</sub> x

wherein x represents the degree of...

...believed to be commonly in the range of from about 30 to about 50,000.

**Chitosan** is not a single, definite chemical entity but varies in composition depending on the conditions of manufacture. It may be equally defined as **chitin** sufficiently deacetylated to form soluble amine salts. **Chitosan** is the beta-(1-4) **polysaccharide** of D- **glucosamine**, and is structurally similar to cellulose, except that the C-2 hydroxyl group in cellulose is substituted with a primary amine group in **chitosan**. The large number of free amine groups makes **chitosan** a polymeric weak base. Solutions of **chitosan** are generally highly viscous, resembling those of natural gums.

The **chitosan** used herein is suitably in relatively pure form. Methods for the manufacture of pure **chitosan** are well known. Generally, **chitin** is milled into a powder and demineralized with an organic acid such as acetic acid...

...lipids are then removed by treatment with a base, such as sodium hydroxide, followed by **chitin** deacetylation by treatment with concentrated base, such as 40 percent sodium hydroxide. The **chitosan** formed is washed with water until the desired pH is reached.

The properties of **chitosan** relate to its polyelectrolyte and polymeric carbohydrate character. Thus, it is generally insoluble in water...

...acids, except, for example, sulfuric acid. In general, the amount of

acid required to dissolve **chitosan** is approximately stoichiometric with the amino groups. Since the pKa for the amino groups present in **chitosan** is between 6.0 and 7.0, they can be protonated in very dilute acids...

...to this biopolymer.

This cationic nature is the basis of many of the benefits of **chitosan**. Indeed, **chitosan** material can be considered as a linear polyelectrolyte with a high charge density...

...with absorbent gelling materials, namely anionic absorbent gelling materials if present in the pad.

Although **chitosan** material might be used as the sole fluid control material in the breast pads herein it might be used in a preferred embodiment of the present invention in combination with absorbent gelling material, to provide outstanding overall fluid absorption properties. Indeed, the use of **chitosan** materials together with anionic absorbent gelling materials, preferably anionic synthetic absorbent gelling materials, in breast pads provides improved absorbing performance not only towards water but especially towards electrolyte-containing fluids like...

...the topsheet. Thus such combination participate to further enhanced comfort and protection in use.

Preferred **chitosan** materials for use herein have an average degree of deacetylation (D.A.) of more than...

...UVNIR, IR, and NIVIR spectroscopy.

The degree of deacetylation will influence the cationic properties of **Chitosan**. By increasing the degree of deacetylation the cationic character of **chitosan** materials will increase and thus their antimicrobial properties, their absorbing ability and gelifying ability.

**Chitosan** materials (i.e., **chitosan** and - **chitosan** salts, modified **chitosans** and cross-linked **chitosans**) may generally have a wide range of molecular weights.

**Chitosan** materials with a wide range of molecular weights are suitable for use in the present invention, typically **chitosan** materials for use herein have a molecular weight ranging from 1 000 to 1 0...

...weight means weight average molecular weight. Methods for determining the weight average molecular weight of **chitosan** materials are known to those skilled in the art. Typical methods include for example light...

...gel permeation chromatography. It is generally most convenient to express the molecular weight of a **chitosan** material in terms of its viscosity in a 1.0 weight percent aqueous solution at...

...C with a Brookfield viscometer. It is common to indirectly measure the viscosity of the **chitosan** material by measuring the viscosity of a corresponding **chitosan** salt, such as by using a 1.0 weight percent acetic acid aqueous solution. **Chitosan** materials suitable for use in the present invention will suitably have a viscosity in a...

...centipoise) and most suitably from 100 mPas (100 centipoise) to about 500 mPas (500 centipoise).

Chitosan materials pH depends on the preparation of the chitosan materials.

Preferred chitosan materials for use herein have an acidic pH, typically in the range of 4 to...

...from 4.5 to 5 Highly preferred pH is around pH5, which corresponds to the skin pH. By

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pH of chitosan material' it is meant herein the pH of a 1 % chitosan solution (1 gram of chitosan material dissolved in 100 grams of distilled water) measured by pH-meter.

Chitosan materials with acidic pH are preferred herein as the cationic character of acidic chitosan materials will be increased and thus their antimicrobial properties, odour and fluid absorbing ability and gelifying ability. However too high acidity is detrimental to skin safety. Thus it is highly preferred herein to use chitosan materials with a pH in the range of 4.5 to 5.5, thereby delivering the best compromise between odor control and fluid handling properties on one side and skin compatibility on the other side.

Particularly suitable chitosan materials for use herein are chitosan salts, especially water soluble chitosan salts. A variety of acids can be used for forming chitosan salts. Suitable acids for use are soluble in water or partially soluble in water, are sufficiently acidic to form the ammonium salt of chitosan and yet not sufficiently acidic to cause hydrolysis of chitosan, and are present in amount sufficient to protonate the reactive sites of chitosan.

Preferred acids can be represented by the formula.

$R-(COOH)_n$

wherein n has a...

...acid, fumaric acid, glycolic acid, iminodiacetic acid, itaconic acid, lactic acid, maleic acid, malic acid, nicotinic acid, 2-pyrrolidone carboxylic acid, salicylic acid, succinamic acid, succinic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, malonic acid, pyruvic acid, sulfonyldiacetic acid, benzoic acid,

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epoxysuccinic acid, adipic acid, thiodiacetic acid and thioglycolic acid. Any chitosan salt formed from the reaction of chitosan with any of these acids are suitable for use herein.

Examples of chitosan salts formed with an inorganic acid include, but are not limited to, chitosan hydrochloride, chitosan hydrobromide, chitosan phosphate, chitosan sulphonate, chitosan chlorosulphonate, chitosan chloroacetate and mixtures thereof. Examples of chitosan salts formed with an organic acid include, but are not limited to, chitosan formate, chitosan acetate, chitosan lactate, chitosan glycolate, chitosan malonate, chitosan epoxysuccinate, chitosan benzoate, chitosan adipate, chitosan citrate, chitosan salicylate, chitosan propionate, chitosan nitrilotriacetate, chitosan itaconate, chitosan hydroxyacetate, chitosan butyrate, chitosan isobutyrate, chitosan acrylate, and mixtures thereof.

It is also suitable to form a chitosan salt ...using a mixture of acids including, for example, both inorganic and organic acids.

Highly preferred chitosan salts for use herein are those formed by the



reaction of **chitosan** with an amino acid. Aminoacids are molecules containing both an acidic and amino functional group. The use of aminoacids instead of other acids, is highly preferred as those **chitosan** amino salts have higher **skin** compatibility.

Indeed most of the aminoacids are naturally present on the **skin** . **Chitosan** salts of pyrrolidone carboxylic acid are effective moisturizing agents and are non irritating to **skin** .

Amino acids for use herein include both linear and/or cyclo amino acids.

Examples of...

...as per following formula.

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CH<sub>2</sub> CH?

Cti? C@o

Z

N

H

Highly preferred **chitosan** salts are **chitosan** pyroglutarnate salt, which is a mixture of **chitosan** (a macromolecule) and pyroglutamic acid (independent monomers), chitosonium pyrrolidone carboxylate, which is the **chitosan** salt of 2pyrrolidone carboxylic acid.

Reference is made to W098/07618 which describes in details processes for the preparation of such **chitosan** salts.

Other **chitosan** materials suitable for use herein include cross-linked **chitosans** and modified **chitosans** .

Crosslinking agents suitable for use in the present invention are generally watersoluble and do not substantially reduce the antimicrobial properties of **chitosan** .

One suitable crosslinking agent is an organic compound having at least two functional groups or functionalities capable of reacting with active groups located on the **chitosan** materials. Examples of such active groups include, but are not limited to, carboxylic acid (-COOH...

...polycarboxylic acids, polyoxides and the like. One way to introduce a crosslinking agent with the **chitosan** solution is to mix the crosslinking agent with **chitosan** during preparation of the solution. Another suitable crosslinking agent comprises a metal ion with more...

...34charges, such as AL , Fe , Ce , Ce , Ti",Zr , and Cr . Since the cations on **chitosan** possess antimicrobial properties, it is preferred herein to not use a crosslinking agent reacting to...

...is from 0.001 to 30 weight percent based on the total dry weight of **chitosan** used to prepare the crosslinked- **chitosan** , more specifically from 0.02 to 20 weight percent, more specifically from 0.05 to 10 weight percent and most preferably from 0.1 to 5 weight percent.

Modified **chitosans** for use herein are any **chitosan** where the glucan chains carry pendant groups. Examples of such modified **chitosans** include carboxymethyl **chitosan** , methyl pyrrolidinone **chitosan** , glycol

chitosan and the like. Methyl pyrrolidone chitosan is for instance described in US 5 378 472, incorporated herein by reference. Water soluble glycol chitosan and carboxymethyl chitosan are for instance described in W087/07618, incorporated herein by reference. Particularly suitable modified chitosans for use herein include water soluble covalently bonded chitosan derivatives or ionically bonded chitosan derivatives obtained by contacting salt of chitosan with electrophilic organic reagents. Such water soluble chitosan derivatives are described in EP-A 737 692, which is herein incorporated by reference.

Suitable chitosan materials for use herein are commercially available from numerous vendors. Exemplary of a commercially available chitosan materials are those available from for example the Vanson Company. The preferred chitosan salt for use herein is chitosan pyrrolidone carboxylate (also called chitosonium pyrrolidone carboxylate) which has a degree of deacetylation of more...

...and one atmosphere), a pH of 4.5 and a viscosity between 100-300 cps.

Chitosan pyrrolidone carboxylate is commercially available under the name Kytamer® PC from Arnerchol Corporation.

Typically, the breast pads might comprise chitosan material or a mixture thereof at a level of from 0.1 gm-2 to...

...4 gm-2 to 30gm

Sh, -)rea@

90P and qpnmptrV of tbe.

Advantageously the breast pads herein because they are made of conformable

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material can be shaped before or during...

...a configuration to fit the woman breast by elastic and/or plastic deformation.

The breast pads might be circular (including circle to ellipsoidal forms). In a preferred execution the pad has a geometry so that at least more than 50% of the surface area of the pad is disposed beneath the breast nipple. With such a pad configuration (see Figures 3 and 4) it is possible to achieve a more discreet and...

...diminished considerably. Accordingly in such an embodiment the topsheet, backsheet and absorbent core constituting the pad are substantially triangular in shape. The substantially triangular type shape is meant to cover all geometries from a simple triangle to pads having flaps extending from each of the three corners.

In the preferred embodiment herein the...

...a configuration to fit the woman breast before or during the manufacturing process of the pad. With this embodiment, the user will avoid the inconvenience of having to shape the pads, and it is possible especially when choosing a radius of curvature for the breast pad less than the natural radius of curvature of the breast to ensure that the pressure from the breast pad will mainly lie outside of the nipple area, at the same time as the breast pad lies in abutment with the breast with an anatomical curvature. A further way of avoiding the nipple from being subjected to pressure is when the central portion of the pad according to the invention includes a depression adapted to

receive the breast nipple.

In a highly preferred embodiment the breast pad is shaped in 3D configuration with a given radius of curvature, this radius being either uniform in all directions (from nipple area to outer edges of the breast pad) or non uniform, e.g., different radius of curvatures can be envisaged in different directions of the breast pad. Preferably the radius of curvatures are different in the horizontal and vertical planes of the breast pad so as to better adapt to the various anatomies of women breast.

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The vaulted or arched triradial and preferably asymmetrical shape of the breast pad is considerably better with regard to stay in place. Further the use of the material...

...described herein in combination with such a shape provides a softer and more pleasant breast pad capable of following the movements of the breast in a more natural manner.

It is...

...is provided with circular pre-scoring lines directed towards the center (nipple area of the pad) such that the garment facing surface of the absorbent core on the periphery/outer edge more readily fold towards the center of the pad (scoring would be on the garment facing side of the absorbent core). If the breast pad is made from a continuous band of a laminate of all material then scoring can...

...product rather than just the core. This would further help the conformability of the breast pads

Rrp,qst Dad construction

In one embodiment the absorbent core of the breast pad extends to the periphery/outer edges of the breast pads, namely the topsheet and backsheet.

In the preferred embodiment the topsheet and the backsheet have...

...core, where they are associated together in a suitable manner.

Adjacent layers of the breast pads might be joined by any suitable manner, including any attachments means known to those skilled...

...e. nipple area). The surface free of adhesive in the central area of the breast pad helps to avoid the strike through of the liquid from the core to the bra...

...Optional non slip properties

According to the present invention the wearer facing surface of the pad and/or the garment facing surface of the pad can be provided with non-slip properties.

In its broadest aspect the present invention also encompasses a breathable breast pad (typically a breast pad having a water vapor permeability higher than 100(g)/(m<sup>2</sup>/24hrs) as defined herein and/or an air permeability higher than 50l/m<sup>2</sup>/s (as defined herein) ), the breast pad having a wearer facing surface and a garment facing surface, wherein at least one of...

...friction greater than 1.

The term 'non-slip' is generally used herein to describe breast pad according to the present invention having at least one outer surface of the breast pad, i.e., the

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wearer facing surface and/or the garment facing surface, typically the...

...treated so as to result in substantially reduced slippage when used in contact against human skin and/or bra/garment. The static coefficient of ...measurements made according to this ASTM test method between the outer surface of the breast pad and a metallic plane covered by a reference material that is white 100% cotton weave...

...the coefficient of friction defined herein when applied on an outer surface of the breast pad.

The non-slip materials suitable to use herein include, but are not limited to, materials...

...coating materials in continuous application on the outer surface of the backsheet of a breast pad the water vapor permeability of the backsheet of the breast pad is reduced only to a minimum extent or even not reduced at all. In other...

...vapor through their 0 thickness. Such elastomers containing urethane bonds include silicones (e.g., heat-cured silicones, condensation-cured silicones and RTV silicones) polyurethanes. A preferred elastomer is RTV 863 from GE Silicones, Inc...

...upon accidental wet/soil through occurrence). Also such copolymer based materials have the ability to cure at room temperature. In other words crosslinking of the copolymer based material will not be...achieve the required dry binder add on to the support layer like nonwoven. Drying and curing of the polymer dispersion is achieved by the application of heat, typically by passing the...

...The non-slip coating materials might be applied onto the outer surface of the breast pad in any conventional way, being continuous or discontinuous. By 'discontinuous' application it is meant herein that portions of the outer surface of the breast pad are left uncoated by the non-slip material. These uncoated portions therefore may contribute to...

...of the surface area of the total surface of the outer surface of the breast pad, preferably having a size and distribution appropriate to cover between at least 1 % and 98% of the total surface area of the outer surface of the breast pad (i.e., the wearer facing surface and/or garment facing surface of the breast pad), typically topsheet and/or backsheet to which it is applied to. More preferably the non...

...to 85% of the total surface area of backsheet and/or topsheet of the breast pad and more preferably between 10% and 70%.

In one embodiment herein wherein a discontinuous pattern of non-slip material is applied onto an outer surface of the breast pad, the pattern selected for the application of the non-slip material may intentionally be directionally...

...The Vapor permeability test is utilized to quantify the vapor transmission properties of breathable breast pads.

132sir Principle of the Methods

The basic principle of the test is to quantify the extent of water vapor

transmission of a breast pad . The test method that is ...PermetghilotV tPst

The air permeability test is utilized to assess the ability of a breast pad to circulation/exchange air.

#### Basic PrincipIp of the Methods

The basic principle of the test is to evaluate the resistance of a breast pad to the passage of air. In this test, the volume (or amount) of air that flows through a breast pad of given dimensions under standard conditions (of 23'C /50% RH) is measured. The instrument...

...test environment for at least 4 hrs prior to commencement of the measurement. The breast pad (having dimensions exceeding 5 cm<sup>2</sup> the dimensions of the measurement head) is placed with the...

...aspiration pump set to generate a pressure of 1210 Pa that sucks air through the pad structure.

The device measures the volume of air flow and the pressure drop across the orifices that contains the pad and measurement head. Finally the device generates a value of air permeability in the units of liters/m<sup>2</sup>/s.

#### Caliper Measurement

The average caliper of the breast pad is determined. The caliper at representative points (at least 5) of the pad is measured to determine an average value by using a micrometer gauge from Lorentzen & Wettre...

...Ocm<sup>2</sup> and pressure of 20g/cm<sup>2</sup>.

#### Conform, ghilitV tPst method

The stiffness of the breast pad is measured according to a modified ASTM method D4032-94, the procedure being performed as...

...2) Numberand preparation of sperimens

In order to perform the procedure for this test five breast pads are necessary.

Each pad is cut with an hydraulic cut to form a circle with a diameter of 49mm...

...method i indpr wpt condition

The tensile strength of the absorbent core of the breast pads herein is measured according to modified ASTM D 5034-95, as described herein.

Tensile strength...water solution

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#### ) Procedure

In order to perform the procedure for this test five breast pads are necessary.

The test method used derives from ASTM (American Standard Test Method) Designation: D...

...Breaking Strength and

Elongation of Textile Fabrics (Grab Test)), and is performed as follows.

Each pad is placed in a 1 inch cutter and one test specimen per pad is cut, the resulting specimen having a wide of one inch (25.4 mm), the length of the specimen corresponding to dimension of the breast pad to be tested. The length of the specimen is not critical provided it is long

...breaking point of the specimen

Ah< ;orr) tgon test

The absorption capacity of the breast pad according to the present invention is determined by the Absorptive capacity test described herein after...

...The present test method differs from ASTM D1 1 1 7-80 in that breast pads are tested, wherein said pads are put floating on the surface of the test fluid without usage of screen, they...

...This test measures the weight of a test fluid which is retained in a breast pad after it is floated on the test fluid for 25 minutes and after applying a static pressure of 17 g/crn2 on the breast pad for 2 minutes.

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) Ins-truments and testincl aids

- Basin 20X20X2cm

- Digital balance accurate to...

...25'25 cm

- Plexiglas Slope with 15o angle to the horizontal (same dimension than the

pad to be tested)

- Weight of 1700g with base dimension 1 0X1 0cm

1 0 (equivalent...

...sliding

3) Test fluid

Saline solution (0.9% NaCl in water)

4) Procedure

The breast pad (overall dimension 93 cm2, caliper 2.5 mm) is pre-weighted using the digital balance...

...fluid in the basin throughout the test is maintained higher than 5 mm.

The breast pad is put in the basin face down (i.e. topsheet down) for 25 minutes.

The breast pad is gently removed from the basin by holding it from its edges. It is left...

...being placed face down on the slope.

The weight is placed gently on the breast pad for 2 minutes (+- 5 sec.) and the arm of the stand is used to fix the weight, thereby avoiding sliding.

The weight is removed after 2 minutes, the breast pad is hold from an edge portion and left to drip in a vertical position for...

...should be followed during the test to ensure consistent accuracy of the results.

The breast pad should be kept flat without bending or twisting in all steps of the test.

The breast pad should be held gently at the top while the load is applied to prevent it...

...slope and base of the weight are to be dry before placement of the breast pad . Also the balance tray should be dry before weighting the wet pad .

#### 5) Evaluation

Absorption Capacity (g)= wet weight (g) - the initial dry weight (g)

The total...

...above

The absorption capacity can be reported in grams per square cm of the breast pad tested as well as in grams per gram of breast pad tested.

The present invention will be illustrated by the following examples

#### Example-I

A triangular shape breast pad 10 (caliper of 2.5 mm) is provided in Figures 3 and 4 and...

...material code: Sawabond  
4124@.

The nonwoven is positioned on the outer side of the breast pad 10, the garment facing side 70. The topsheet and the backsheet are sealed together into...

...H. Sandier GmBh& Co.KG under material code: Sawabond 4124@.

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#### Example 2

A breast pad as described in Example I is made except that the nonwoven backsheet is provided with...

...nonwoven already coated to the  
0 thermoplastic film before incorporating the backsheet in the breast pad . The spray operation is conducted at room temperature (23°C +-2°C) by spraying  
21.73g/m<sup>2</sup>...

...8.8g/m<sup>2</sup> (dry polymer) after  
drying at room temperature.

#### Example 3

A circular breast pad (diameter 10.5 cm and caliper of 2.5 mm) has been made as follow...

...material code- Sawabond 41240.

The nonwoven is positioned on the outer side of the breast pad , the garment facing side. The topsheet and the backsheet are sealed together into a peripheral...is the same as those described herein in Example 1 above.

Fx,qmaLaA

A breast pad as described in Example 3 is made except that the nonwoven backsheet is provided with...

...the nonwoven already coated to the  
thermoplastic film before incorporating the backsheet in the breast pad . The spray operation is conducted at room temperature (23°C +-2°C) by spraying 21.73g/m<sup>2</sup>...

...in Figures 1 and 2 and comprises (as seen in Figure 1-cross section of

pad construction).

- a topsheet 2, namely a spunbonded, surfactant treated polyethylene nonwoven commercially available from BBA...

...positioned between the absorbent core and the first layer backsheet layer.

Fx2mple 6

A breast pad as described in Example 5 is made except that the nonwoven backsheet is provided with...

...resulting solution is sprayed onto the nonwoven backsheet before it is incorporated into the breast pad. The spray operation is conducted at room

temperature (230C +-2oC) by spraying 21.73g/m2...

...drying at room temperature.

T2h]e

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Below table is a comparison table between breast pads according to the present invention namely those exemplified in Examples 4 and 6 described herein versus commercially available competitive breast pads.

Different parameters are compared. This table is indicative. It is understood herein that the scope of the present invention is not limited to the breast pads exemplified herein nor to the parameters compared in this table.

This table compares breast pads illustrated herein before in Examples 4 and 6 to breast pads commercially available namely (1) from Johnson & Johnson under the trade name "Healthflow Ultra Nursing Pad" Safeway Denver Co, (2) Gerber under the trade name "Super Absorbent Nursing Pad" on the US market and (3) under the name 'Pigeon breast pad' by Santo Health Care Products for their comformability properties (stiffness under modified ASTIVI method D4032-94 described herein...

...per ASTIVI E 96 - 80 test method mentioned herein before), integrity properties of the breast pads (tensile strength under wet conditions of the absorbent core as per modified ASTIVI D 5034...

...described herein before) caliper and coefficient of friction (as per ASTIVI D 1894).

(1) Breast pad available from Johnson & Johnson is made of a spunlaced nonwoven and aifelt absorbent core and a nonwoven backsheet, this pad is free of super absorbent gelling material (AGM).

(2) Breast pad available from Gerber is made of an airfelt with synthetic fibers as an absorbent core, sandwiched between a thermalbonded nonwoven topsheet and a nonwoven backsheet, this pad is free of super absorbent gelling material (AG M).

0

(3) Pigeon breast pad is made of an absorbent core made of airfelt with AGM powder sandwiched between wetlaid...

...a non breathable polyethylene/wetlaid



nonwoven and fastening adhesive and release paper.

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Breast Breast Healthflo Super Pigeon  
pad of pad of w Ultra Absorbent breast pad

Example Example Nursing Nursing

4 6 Pad -J&J Pad

Gerber

Stiffness q 308 250 1940 627 325

WVTR g/(M2 /24 400 592 896...

#### Claim

1 A disposable thin breathable breast pad having a wearer facing surface and a garment facing surface, said breast pad having a water vapor permeability of more than 1 00 (g) / (m'/24hrs) and a stiffness of less than 600 grams.

2 A pad according to claim 1, having a water vapor permeability of more than 1 00 (g...

...M2 /24 hrs), and most preferably higher than 300 (g) / (M2 / 24 hrs).

3 A pad according to any of the preceding claims having a stiffness of less than 500 grams...

...preferably less than 400 grams, and most preferably of less than 350 grams.

4 A pad according to any of the preceding claims having a fluid absorption capacity of at least...

...80 and most preferably from 0.25 to 0.6 grams per CM2.

5 A pad according to any of the preceding claims having a thickness of less than 5.0...

...0.5 mm and most preferably from 3.0 to 1.0 mm.

6 A pad according to any of the preceding claims wherein the wearer facing surface and/or the garment facing surface of the pad has a coefficient of friction greater than 1 .

7 A pad according to any of the preceding claims wherein said pad comprises

a liquid permeable and water vapour pervious topsheet, a liquid impermeable, water vapour permeable backsheet and an absorbent core disposed between said topsheet and said backsheet.

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. A pad according to claim 7 wherein said absorbent core has a tensile strength under wet condition...

...g/25.4mm and more preferably from 1500 to 4000 g/25.4mm.

9 A pad according to any of the preceding claims 7 or 8 wherein said absorbent core typically...

...and non granular super absorbent gelling material, preferably fibrous super absorbent gelling material.

10 A pad according to claim 9 wherein the absorbent core comprises from

0.1% to 95%, preferably...

...10% to

55% by weight of the non granular super absorbent gelling material.

11 A pad according to any of the preceding claims 7 to 10 wherein said backsheet is a...

...vapour permeable composite

structure comprising a hydrophilic thermoplastic film and a support layer.

12 A pad according to claim 11, wherein said thermoplastic film comprises from 5% to 100% by weight of a polymer or mixture of polymers.

13 A pad according to claim 12, wherein said polymer is selected from the group consisting of polyurethanes...

...and derivatives, polyvinyl pyrrolidone

and its copolymers, thermoplastic cellulose derivatives, and mixtures thereof.

14 A pad according to any of the claims 11 to 13 wherein said hydrophilic

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thermoplastic...

...esters, phosphates,

monocarboxylic fatty acids (C8-C22) and their derivatives, and mixtures thereof.

15 A pad according to any of the claims 11 to 14 wherein said hydrophilic thermoplastic film...

...preferably from 2% to 15% by weight of a blend of tackifier resins.

16 A pad according to any of the claims 11 to 15 wherein the support layer of...

...structure is selected from the group consisting of wovens, nonwovens and apertured films.

17 A pad according to any of the preceding claims 1 to 10 wherein the garment facing...

...100 I/M2/S, and more preferably higher than 200 I/M2/S.

18 A pad according to claim 17 wherein the backsheet comprises at least a first layer made of...

...basis weight of less than 100 g/m2 and preferably less than 50.

19 A pad according to any of the preceding claims further comprising chitosan material or a mixture thereof preferably at a level of from 0.1 gm-2...

...2 and most preferably from 4 gm-2 to 50 gm

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. A breathable breast pad having a wearer facing surface and a garment facing surface, wherein at least one of said surfaces has a coefficient

of  
friction greater than 1.

21 A pad according to any of the preceding claims 6 or 20 wherein at least one of...

15/3,K/6 (Item 6 from file: 349)  
DIALOG(R)File 349:PCT FULLTEXT  
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00847657 \*\*Image available\*\*

**BREATHABLE ABSORBENT ARTICLES COMPRISING CHITOSAN MATERIAL**  
**ARTICLES ABSORBANTS IMPER-RESPIRANTS COMPRENANT DU CHITOSAN**

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Detailed Description

Claims

English Abstract

The present invention relates to breathable absorbent articles, such as  
sanitary napkins, pantliners, nursing pads and baby diapers, having a  
breathable backsheet, and comprising a **chitosan** material. Absorbent  
articles are provided that deliver not only initial high performing  
breathability but also...

French Abstract

...des couches, possedant une couche inferieure imper-respirante et  
contenant un materiau a base de **chitosan**. Ces articles absorbants non  
seulement presentent une capacite d'imper-respiration initiale elevee  
mais conservent...

Detailed Description

BREATHABLE ABSORBENT ARTICLES

C-1-P  
of  
PCT  
FILE  
DATE  
23 APRIL 2001  
EP  
FILE DATE  
25 APRIL  
2000

Claim  
4 !!

## COMPRISING CHITOSAN MATERIAL

### Field of the Invention

The present invention relates to absorbent articles in particular sanitary...

...breathable absorbent article, particularly by the provision of a breathable backsheet, which article comprises a **chitosan** material. (inverted exclamation mark)t has only now been found that the use of **chitosan** materials in disposable breathable absorbent articles can provide an unexpected benefit in respect to maintaining effective breathability of the articles during prolonged usage conditions.

**Chitosan** materials have the ability to instantaneously reduce fluid diffusion once they are contacted with bodily...

...of the stains of menses in the articles). In other words the presence of a **chitosan** material in an absorbent article will result in larger area of dry article ( pad ), which is not soiled by bodily fluids like menses. Advantageously the concentration of the bodily...

...to be bound by any theory, this benefit is obtained due to the properties of **chitosan** material to instantaneously gelify bodily fluids coming into contact with (inverted exclamation mark)t. The gelification rate of **chitosan** material is only a few seconds towards bodily fluids, i.e., organic fluids like menses. The positively charged cationic groups of the **chitosan** materials will interact with negatively charged anionic functionalities present in bodily fluids, like the carboxylic...

...acid). This will result in the formation of tridimensional net between cationic function of the **chitosan** materials and such molecules with anionic groups. This rapid physical change of the bodily fluid...

...(inverted exclamation mark)t in the article avoiding fluid transfer.

Advantageously the presence of **chitosan** material, alone or in combination with an anionic absorbent gelling material like polyacrylate, allows to...

...materials) which comprises for example only such an anionic absorbent gelling material in absence of **chitosan** material at the same total level

The purpose of the present invention is preferably achieved...

...air) is measured in accordance with the air permeability test disclosed herein after.

By selecting **chitosan** materials and using them in breathable absorbent articles not only improved physical comfort to the...

...reduction.

Without to be bound by any theory (inverted exclamation mark)t is believed that **chitosan** materials provide fluid absorption and odor control of malodorous components associated with bodily fluid by multiple mechanisms.

Firstly, the odor and fluid absorption and retention characteristics of **chitosan** materials - due to the presence in the polymer structure of ionisable cationic functional groups. These...

...permits absorption of molecules (malodor and fluid).

Secondly, the positively charged cationic groups of the **chitosan** materials will interact with negatively charged anionic group-bearing molecules present in

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bodily fluids...

...which will entrap most molecules (like lipids, acids) thereby retaining fluid and malodor.

Thirdly the **chitosan** materials are believed to act as antimicrobial agents. Indeed the **chitosan** material with its positively charged cationic groups will interfere with negatively charged surface of microorganism walls, thereby inhibiting the growth of such microorganisms or even killing such microorganisms. The **chitosan**

material will also interfere with negatively charged surface of enzymes, thereby inactivating the enzymatic activity, which, like the microbial activity, are otherwise responsible for the formation of malodorous components. The **chitosan** materials further act by their indirect antimicrobial activity by linking some of the microorganism nutrients...

...the

breathability of the article, which reduces the hot, humid and anaerobic environment between the **skin** of the wearer and the surface of the absorbent article, contributes in an overall reduction...

...fluid. The reduction in the hot, humid and occlusive environment between the vicinity of the **skin** of the wearer and the article itself also reduces the tendency of the wearer to...

...generated within the absorbent article.

In a particularly suitable embodiment of the present invention the **chitosan** material is located in the core of the absorbent article directed towards the backsheet (Le...

...of odor and fluid leakage through the breathable backsheet.

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Advantageously the use of **chitosan** material is compatible with **skin** safety.

Indeed, the cationic properties of **chitosan** materials allow binding to the negatively charged surface of the **skin**, typically in the case of rewetting occurrence (where **chitosan** can be brought in contact with the **skin** through bodily fluid transport), thereby moisturizing the **skin** and providing a long lasting softness and fullness.

Also **chitosan** material has been found to be particularly suitable for absorbent articles like breast **pads** as an effective material for absorbing lactational fluids. Indeed the use of **chitosan** material in breast **pads** /nursing **pads** provides effective fluid absorption towards lactational fluids, Le. fluids containing a high proportion of electrolytes...would interfere with usually used gelling absorbent materials like polyacrylates. Also the antimicrobial activity of **chitosan** material will prevent the formation of **skin** irritation or even breast infection while being safe to babies. Thus in its broader aspect, the present invention also encompasses nursing **pads** comprising

chitosan material.

Background art of the invention

The incorporation of breathable backsheets in absorbent articles for...

...392 discloses breathable absorbent articles having a chelating agent based odor control system.

Articles comprising chitosan materials are known from the art. For example W099/32697 discloses that chitosan and chitin -based polymers exhibit increased antimicrobial activity when coated onto the surface of a hydrophobic material...

...None of these prior art references suggests the benefit of providing breathable absorbent articles comprising chitosan materials, namely those of providing absorbent articles that combine high breathable performance for comfort even...

...an absorbent core comprising a first and a second tissue layers forming a laminate, the chitosan material is incorporated between said first and second tissue layers.

Figure 2 shows a cross...

...backsheet and an absorbent core comprising a first and a second tissue layers, wherein the chitosan material is located on the inner side of the second tissue (inverted exclamation mark)ayer...

...breathable backsheet and an absorbent core comprising a first and a second tissue layers, wherein chitosan material together with absorbent gelling material are located between said first and second tissue layers ...

...the absorbent gelling material are distributed between the first and second tissue layers and wherein chitosan material is applied onto the inner surface of the second tissue (inverted exclamation mark)ayer...

...an absorbent article suitable for absorbing bodily fluid, having a breathable backsheet and comprising a chitosan material.

The present invention also encompasses the use of chitosan material in a breathable absorbent article suitable for absorbing bodily fluid, comprising a (inverted exclamation mark)ayer...

...invention relates to breathable absorbent articles such as sanitary napkins, panty liners, incontinence devices, nursing pads /breast pads and baby diapers, interlabial pads . Typically such products comprise a liquid pervious topsheet, a backsheet and an absorbent core intermediate ...

...including for instance perspiration, urine, menstrual fluids, faeces, vaginal secretions, lactational fluid and the like.

#### Chitosan materials

According to the present invention the articles comprise as an essential component a chitosan material or a mixture thereof.

By 'chitosan material' (inverted exclamation mark)t is meant herein chitosans , modified chitosans , crosslinked chitosans and chitosan salts.

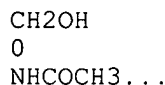
**Chitosan** is a partially or fully deacetylated form of **chitin**, a naturally occurring polysaccharide. Indeed, **chitosan** is an aminopolysaccharide usually prepared by deacetylation of **chitin** (poly-beta(1 4)-N-acetyl-D-glucosamine).

**Chitin** occurs widely in nature, for example, in the cell walls of fungi and the hard...

...from shrimp-, lobster, and crab seafood industries typically contains about 10 to about 15 percent **chitin** and is a readily available source of supply. In the natural state, **chitin** generally occurs only in small flakes or short fibrous material, such as from the carapace...

...that forms useful shaped articles without solution and re-precipitation or re-naturing.

More specifically, **chitin** is a mucopolysaccharide, poly-N-acetyl-D-glucosamine with the following formula.



...believed to be commonly in the range of from about 30 to about 50,000.

**Chitosan** is not a single, definite chemical entity but varies in composition depending on the conditions of manufacture. (inverted exclamation mark)t may be equally defined as **chitin** sufficiently deacetylated to form soluble amine salts. **Chitosan** is the beta-(1-4) **polysaccharide** of D- **glucosamine**, and is structurally similar to cellulose, except that the C-2 hydroxyl group in cellulose is substituted with a primary amine group in **chitosan**. The large number of free amine groups makes **chitosan** a polymeric weak base. Solutions of **chitosan** are generally highly viscous, resembling those of natural gums.

The **chitosan** used herein is suitably in relatively pure form. Methods for the manufacture of pure **chitosan** are well known. Generally, **chitin** is milled into a powder and dematerialized with an organic acid such as acetic ...lipids are then removed by treatment with a base, such as sodium hydroxide, followed by **chitin** deacetylation by treatment with concentrated base, such as 40 percent sodium hydroxide. The **chitosan** formed is washed with water until the desired pH is reached.

The properties of **chitosan** relate to its polyelectrolyte and polymeric carbohydrate character. Thus, (inverted exclamation mark)t is generally ...

...acids, except, for example, sulfuric acid. In general, the amount of acid required to dissolve **chitosan** is approximately stoichiometric with the amino groups. Since the pKa for the amino groups present in **chitosan** is between 6.0 and 7.0, they can be protonated in very dilute acids...

...to this biopolymer.

This cationic nature is the basis of many of the benefits of **chitosan**. Indeed, **chitosan** material can be considered as a linear polyelectrolyte with a high charge density which can...

...embodiment of the present invention wherein anionic absorbent gelling material are present on top of **chitosan**, thereby further enhancing the



odor control properties of the **chitosan** materials and providing enhanced fluid absorption properties).

Preferred **chitosan** materials for use herein have an average degree of deacetylation (D.A.) of more than...

...VIS, IR, and NIVIR spectroscopy.

The degree of deacetylation will influence the cationic properties of **chitosan**. By increasing the degree of deacetylation the cationic character of **chitosan** materials will increase and thus their antimicrobial properties, their absorbing ability and gelifying ability.

Suitable **chitosan** materials to use herein include both water-soluble and water insoluble **chitosan**. As used herein, a material will be considered to be watersoluble when it substantially dissolves...

...losing its initially particulate form and becoming essentially molecularly dispersed throughout the water solution. Preferred **chitosan** materials for use herein are water soluble, Le., at least 0.5 gram, preferably at least 1 gram

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and more preferably at least 2 grams of the **chitosan** materials are soluble in 100 grams of water at 250C and one atmosphere. By solubility ...

...250C and one atmosphere in absence of precipitate.

As a general rule, the water-soluble **chitosan** materials will be free from a substantial degree of crosslinking, as crosslinking tends to render the **chitosan** materials water insoluble.

Water-soluble **chitosan** materials as defined herein are preferred as they have the benefit to be more active...

...of the malodorous compounds present and soluble in the bodily fluid. Indeed such water-soluble **chitosan** materials have the ability to absorb and/or electrostatically interfere with water-soluble malodorous components...

...e.g., butyric acid) or low molecular weight alcohol (e.g., ethanol). Also water-soluble **chitosan** materials have the ability to chelate most of the metals necessary to bacterial growth (e.g., Calcium, Zinc).

**Chitosan** materials (Le., **chitosan** and - **chitosan** salts, modified **chitosans** and cross-linked **chitosan**) may generally have a wide range of molecular weights.

**Chitosan** materials with a wide range of molecular weights are suitable for use in the present invention, typically **chitosan** materials for use herein have a molecular weight ranging from 1 000 to 10 000...

...weight means weight average molecular weight. Methods for determining the weight average molecular weight of **chitosan** materials are known to those skilled in the art. Typical methods include for example light...

...inverted exclamation mark) it is generally most convenient to express the molecular weight of a **chitosan** material in terms of its viscosity in a 1.0 weight percent aqueous solution at 250C with a Broodeld viscometer.

It is common to indirectly measure the viscosity of the chitosan material by measuring the viscosity of a corresponding chitosan salt, such as by using a 1.0 weight percent acetic acid aqueous solution. Chitosan materials suitable for use in the present invention will suitably have a viscosity in a...

...from 1 00 mPa. s (1 00 centipoise) to about 500 mPa- s (500 centipoise).

Chitosan materials pH depends on the preparation of the chitosan materials.

Preferred chitosan materials for use herein have an acidic pH, typically in the range of 4 to...

...4.5 to 5 Highly preferred pH is around pH 5, which corresponds to the skin pH. By 'pH of chitosan material' (inverted exclamation mark)t is meant herein the pH of a 1 % chitosan solution (1 gram of chitosan material dissolved in 100 grams of distilled water) measured by pH-meter.

Chitosan materials with acidic pH are preferred herein as the cationic character of acidic chitosan materials will be increased and thus their antimicrobial properties, odor and fluid absorbing ability and gelify(inverted exclamation mark)ng ability. However too high acidity is detrimental to skin safety. Thus (inverted exclamation mark)t is highly preferred herein to use chitosan materials with a pH in the range of 4.5 to 5.5, thereby delivering the best compromise between odor control and fluid handling properties on one side and skin compatibility on the other side.

Particularly suitable chitosan materials for use herein are chitosan salts, especially water-soluble chitosan salts. A variety of acids can be used for forming chitosan salts. Suitable acids for use are soluble in water or partially soluble in water, are sufficiently acidic to form the ammonium salt of chitosan and yet not sufficiently acidic to cause hydrolysis of chitosan, and are present in amount sufficient to protonate the reactive sites of chitosan.

Preferred acids can be represented by the formula.

$R-(COOH)_n$   
wherein n has a...

...acid, fumaric acid, glycolic acid, iminodiacetic acid, itaconic acid, lactic acid, maleic acid, malic acid, nicotinic acid, 2-pyrrolidone carboxylic acid, salicylic acid, succinamic acid, succinic acid, ascorbic acid, aspartic acid, glutamic acid, glutaric acid, malonic acid, pyruvic acid sulfonyldiacetic acid, benzoic acid, epoxysuccinic acid, adipic acid, thiodiacetic acid and thioglycolic acid. Any chitosan salts formed from the reaction of chitosan with any of these acids are suitable for use herein.

Examples of chitosan salts formed with an inorganic acid include, but are not limited to, chitosan hydrochloride, chitosan hydrobromide, chitosan phosphate, chitosan sulphonate, chitosan chlorosulphonate, chitosan chloroacetate and mixtures thereof. Examples of chitosan salts formed with an organic acid include, but are not limited to, chitosan formate, chitosan acetate, chitosan lactate, chitosan glycolate, chitosan malonate, chitosan epoxysuccinate, chitosan

benzoate, chitosan adipate, chitosan citrate, chitosan salicylate, chitosan propionate, chitosan nitrilotriacetate, chitosan itaconate, chitosan hydroxyacetate, chitosan butyrate, chitosan isobutyrate, chitosan acrylate, and mixtures thereof. It is also suitable to form a chitosan salt using a mixture of acids including, for example, both inorganic and organic acids.

Highly preferred chitosan salts for use herein are those formed by the reaction of chitosan with an amino acid. Amino acids are molecules containing both an acidic and amino functional group. The use of amino acids instead of other acids is highly preferred as those chitosan amino salts have higher skin compatibility.

Indeed most of the amino acids are naturally present on the skin. Chitosan salts of pyrrolidone carboxylic acid are effective moisturizing agents and are nonirritating to skin.

Amino acids for use herein include both linear and/or cyclo amino acids.

Examples of amino...

...pyrrolidinone as per following formula.

13  
H<sub>2</sub>C CH<sub>2</sub>  
C C  
O  
OH

Highly preferred chitosan salts are chitosan pyroglutamate salt, which is a mixture of chitosan (a macromolecule) and pyroglutamic acid (independent monomers), chitosonium pyrrolidone carboxylate, which is the chitosan salt of 2-pyrrolidone carboxylic acid.

Reference is made to W098107618, which describes in details processes for the preparation of such chitosan salts.

Other chitosan materials suitable for use herein include cross-linked chitosans and modified chitosans.

Crosslinking agents suitable for use in the present invention are generally watersoluble and do not substantially reduce the antimicrobial properties of chitosan.

One suitable crosslinking agent is an organic compound having at least two functional groups or functionalities capable of reacting with active groups located on the chitosan materials. Examples of such active groups include, but are not limited to, carboxylic acid (-COOH...

...polycarboxylic acids, polyoxides and the like. One way to introduce a crosslinking agent with the chitosan solution is to mix the crosslinking agent with chitosan during preparation of the solution. Another suitable crosslinking agent comprises a metal ion with more...

...11 Ce 4-1 j Ti4+7 Zr4+, and Cr 3, ". Since the cations on chitosan possess antimicrobial properties, (inverted exclamation mark) it is preferred herein to not use a crosslinking...

...is from 0.001 to 30 weight percent based on the total dry weight of chitosan used to prepare the crosslinked- chitosan, more specifically 14 from 0.02 to 20 weight percent, more specifically from 0.05 to 10 weight

percent and most preferably from 0.1 to 5 weight percent.

Modified **chitosans** for use herein are any **chitosan** where the glucan chains carry pendant groups. Examples of such modified **chitosans** include carboxymethyl **chitosan**, methyl pyrrolidinone **chitosan**, glycol **chitosan** and the like. Methyl pyrrolidone **chitosan** is for instance described in US 5 378 472, incorporated herein by reference. Water-soluble glycol **chitosan** and carboxymethyl **chitosan** are for instance described in WO87/07618, incorporated herein by reference. Particularly suitable modified **chitosans** for use herein include water-soluble covalently bonded **chitosan** derivatives or ionically bonded **chitosan** derivatives obtained by contacting salt of **chitosan** with electrophilic organic reagents. Such water-soluble **chitosan** derivatives are described in EP-A737 692, which is herein incorporated by reference.

Suitable electrophilic organic reagents suitable for use for the preparation of **chitosan** derivatives contain from 2 to 18 carbon atoms or more per molecule and typically from...

...reagent may react with either the free amine or the underivatized hydroxyl groups of the **chitosan**. It is known that the amine functionality of the **chitosan** is generally regarded as a stronger nucleophilic site

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than the hydroxyl groups. Consequently weaker...

...to react more readily with the amine groups than with the hydroxyl groups of the **chitosan**.

Preferably an effective amount of electrophilic organic reagent is substituted onto the **chitosan** to achieve the desired properties of the **chitosan** derivative, namely its water-soluble properties. Typically the **chitosan** derivatives suitable for use herein (modified **chitosan**) have a MS of from 0.03 to 10 moles of the electrophilic organic reagent...

...The term molar substitution (MS), means the moles of electrophilic organic reagent substituted on the **chitosan** per mole of glucosamine monomer unit.

In addition further modified **chitosan** can be prepared which contain other substituent groups, such as hydroxalkyl ether group (e.g. ...

...to the reaction with the electrophilic organic reagent, or introduced simultaneously by reaction of the **chitosan** salt with the electrophilic organic reagent and the other derivatizing reagent.

Typically such covalently bonded **chitosan** derivative might be obtainable by a process which includes the step of (a) dispersing a salt of **chitosan** (e.g., any one of those described herein before) in an effective amount of an aqueous caustic medium to form a neutralized **chitosan** containing free amine groups, (b) introducing an electrophilic organic reagent in the slurry and (c. ...

...temperature and time effective to promote the substitution of the electrophilic organic reagent onto the **chitosan** to form a covalently bonded **chitosan** derivative and the dissolution of the covalently bonded **chitosan** into the aqueous medium. The **chitosan** derivatives can be prepared in either salt form, i.e., ionically bonded, or in the covalently bonded form. Processes for the preparation of such **chitosan** derivatives

are described in depth in EP-A-737 692, incorporated herein by reference.

Suitable **chitosans** are commercially available from numerous vendors.

Exemplary of a commercially available **chitosan** materials are those available from for example the Vanson Company. The preferred **chitosan** salt for use

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herein is **chitosan** pyrrolidone carboxylate (also called chitosonium pyrrolidone carboxylate), which has a degree of deacetylation of more...

...and one

atmosphere), a pH of 4.5 and a viscosity between 100-300 cps. **Chitosan** pyrrolidone carboxylate is commercially available under the name Kytamero PC from Amerchol Corporation.

Typically, the articles like disposable absorbent articles comprise **chitosan** material or a mixture thereof at a level (inverted exclamation mark) of from 0.5...

...50 gm

The present invention is based on the finding that the presence of a **chitosan** material (preferably a **chitosan** salt like chitosonium pyrrolidone carboxylate), in a breathable absorbent article provides not only initial comfort...

...bodily fluids, while providing at the same time high level (inverted exclamation mark) of protection.

**Chitosan** materials have the ability of instantaneously changing the physical properties of bodily fluids. Indeed a...

...question mark) if the bodily fluid is obtained when the fluid comes into contact with **chitosan** material. **Chitosan** material has the advantage of having a high gelification rate. This can be quantified by of **chitosan** material (especially **chitosan** salts as-described herein before) in a breathable absorbent article allows to maintain an effective ...

...17

The articles according to the present invention may further comprise on top of the **chitosan** materials described herein before, other conventional agents or mixtures thereof.

Optional absorbent gelling materials

According...to 100 gm

An anionic absorbent gelling material is suitably used on top of the **chitosan** material herein as it is able to further enhance the advantages of the present invention. Indeed anionic absorbent gelling materials are believed to further enhance the cationic properties of **chitosan** materials. Without to be bound by any theory, (inverted exclamation mark) it is believed that the negatively charged anionic groups of anionic absorbent gelling materials protonate the cationic groups of **chitosan** materials, thereby enhancing their cationic properties. This translates in improved gelification properties, especially further enhanced...

...breathability of the article during loading of bodily fluid. The enhanced cationic properties of the **chitosan** materials further translate in improved odor control properties too.

Advantageously combining anionic absorbent gelling materials...

...herein (typically having a degree

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of neutralization of from 25% to 90%) together with **chitosan** materials, in an absorbent article results in outstanding fluid absorption capacity not only towards water...

...be due to the reduction of the salt poisoning effect associated to the presence of **chitosan** materials beside anionic absorbent gelling material.

Furthermore the use of anionic absorbent gelling materials, namely...

...herein (typically having a degree of neutralization of from 25% to 90%) on top of **chitosan** materials, in an absorbent article, exhibits high gel strength during fluid absorption. Indeed this combination...

...in decreased rewetting and wetting through.

In a preferred embodiment according to the present invention **chitosan** material and the anionic absorbent gelling material are present in the absorbent article at a weight ratio of **chitosan** material to absorbent gelling material of from 10:1 to 1:10, preferably from 5...benefits of the present invention by further enhancing and maintaining the cationic properties of the **chitosan** materials herein, even upon aging of the bodily fluid, Le., upon prolonged wearing time of...

...200 gm-2

The disposable articles

Preferred breathable articles herein are pantliners, feminine napkins, incontinent **pads**, diapers, nursing **pads**, and the like. The **chitosan** material (and optional absorbent gelling material and/or optional additional odor control agent(s)) may...

...such purpose by those skilled in the art.

The articles of the invention may comprise **chitosan** materials, typically **chitosan** material powder, coated **chitosan** material or any other form of **chitosan** material, in any location of such articles. Typically **chitosan** materials may be distributed homogeneously or non-homogeneously in at least one or several layers...

...or in at least one or several (inverted exclamation mark) layers of the core. Also **chitosan** materials may be distributed homogeneously or non-homogeneously on the whole surface of the...

...the edges of a (inverted exclamation mark) layer of the absorbent article) or mixtures thereof.

**Chitosan** material may typically be present in the absorbent core of the absorbent article (also called...

...which is positioned between the topsheet and the backsheet of the absorbent article). More preferably **chitosan** material may be present in the fluid storage (inverted exclamation mark) layer as described herein. The presence of the **chitosan** material in the core is suitable as the core collects and absorbs bodily fluids. In a preferred embodiment of the present invention the **chitosan** material and optional additional agents are typically incorporated between two layers of cellulose tissue,

typically...

...of the laminate to ensure that the edges of the laminate stick and any loose chitosan materials and optional additional agents present do not fall out of the laminate.

In particular embodiments of the present invention chitosan material is present in the absorbent core but directed towards the backsheet. By 'directed towards the backsheet' it is meant that the chitosan material is closer to the backsheet than the topsheet. This can be achieved where the absorbent core comprises laminate by disposing chitosan material on either sides or both sides of the air laid cellulose layer of the laminate, which is facing the backsheet. Typically the chitosan material might be coated or sprayed onto such an air laid (inverted exclamation mark)ayer. Or a chitosan film/(inverted exclamation mark)ayer might be used as suitable layers to form such a laminate. This can be achieved too by disposing chitosan material particle/powder so as to form a gradient concentration through the thickness of the absorbent core, a so called Z-directional gradient, wherein the concentration of the chitosan material increases from the surface of the absorbent core facing the topsheet to the surface...

...of such

constructions are also included herein. In other embodiments of the present invention the chitosan material is located in the backsheet itself (preferably the first layer of the backsheet as...of the bodily fluid comes into contact with said absorbent gelling material before contacting the chitosan material. Such executions are particularly beneficial(inverted exclamation mark) for combining optimum breathability during use...

...retained in close proximity to the absorbing gelling material, thereby reducing the wetting of the chitosan material and thus enhancing its odor control ability. Also the first contact of the fluid...

...of alkaline odorous compounds but also maintaining or even enhancing the cationic properties of the chitosan materials and thus their antimicrobial properties but also their gelification properties. It is further speculated that the chitosan material due to its gelifying properties will have the tendency to retain the fluids and...

...of absorbent gelling material located so that the fluid first contact it before contacting the chitosan material provides further improved odor control and fluid control as well as helps in maintaining...

...and an absorbent core, the article comprising an absorbent gelling material on top of the chitosan material, these materials being located in the absorbent articles such that the bodily fluid first contacts the absorbing gelling material before contacting the chitosan material. This is typically achieved in execution wherein the chitosan material is located beneath the absorbent gelling material (in a vertical superimposed relationship) and/or...

...so called wetting location, typically found in the center of the absorbent article) and the chitosan material is placed in a separate region outside said wetting location for instance in a...

...of the present invention the absorbent gelling material is located towards the topsheet whereas the chitosan material is located towards the backsheet, i.e., the chitosan material is further away from the

topsheet than the absorbent gelling material. Preferably the absorbent gelling material is located in the core and the chitosan material is located further away from the topsheet than the absorbent gelling material. For example when a laminate of two fibrous layers is used as the absorbent core, chitosan material is

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typically the fibrous (inverted exclamation mark)ayer directed towards the backsheet (by...

...Le., the one directed to the topsheet and the one directed to the backsheet). Also chitosan material particies and the absorbent gelling material particles might be incorporated in reverse gradient concentration through the thickness of the absorbent core. This can be achieved by disposing chitosan material particle so as to form a gradient concentration through the thickness of the absorbent core, a so called Z-directional gradient, wherein the concentration of the chitosan materials increases from the surface of the absorbent core facing the topsheet to the surface...

...other embodiments of the present invention, the absorbent gelling material is physically separated from the chitosan material, tpically by being located in a separate (inverted exclamation mark)ayer from the chitosan material. Both materials might be present in the absorbent core but separated by a (inverted...

...Alternatively the absorbent article may comprise the absorbent gelling material in the core and the chitosan material inlon the backsheet, tpically the secondary backsheet.

The chitosan materials as described herein may be incorporated in particle form 2@ as a powder or a granulate. When used in particie form the chitosan materials as described herein and the optional absorbent gelling material and optional odor control agent may be granulated separately and then mixed together or granulated together.

The chitosan material might also be applied onto the desired layer by simply spraying a solution containing chitosan material and letting said (inverted exclamation mark)ayer to dry. This is an easy and cost effective way to introduce chitosan material onto for example a cellulose air laid tissue before the lamination process and thus... secondary distribution layers, is a fluid storage layer. The fluid storage layer can comprise the chitosan material and optional absorbent gelling material. It preferably comprises these materials in combination with suitable...

...other for example by adhesive or by mechanical interlocking or by hydrogen bridge bands. The chitosan material and optional absorbent gelling material and/or other optional material can be comprised between ...

...additional fluid-handling capabilities such as rapid wicking of fluid along the length of the pad .

d Other Optional Components of the absorbent structure

The absorbent core according to the present...layer individually needs to be

compliant, soft feeling, and non-irritating to the wearer's skin . It also can have elastic characteristics allowing it to be stretched in one or two...



...a reduced tendency to allow fluids to pass back through and rewet the wearer's skin. Thus, the surface of the formed film that is in contact with the body remains...

...the absorbent article may find utility as sanitary napkins, panty liners, adult incontinence products, nursing pads and baby diapers. The present invention finds particular susceptibility as sanitary napkins and panty liners...the supplier code Unikay 303 LF}. Between the two tissue layers the laminate contains a **chitosan** material. The **chitosan** material is chitosonium pyrrolidone carboxylate powder, commercially available from Amerchol Corporation, Edison, New Jersey under...release liner 8.

#### Example 2.

Example 2 is identical to Example 1 except that the **chitosan** material is a **chitosan** solution that is sprayed on the fissure air laid layers of the laminate core directed towards the backsheet. The **chitosan** solution can be sprayed on either side of the fissure air laid layer or even on both sides before reconstituting the pantiliner. The **chitosan** solution is prepared by solubilizing 1 g of chitosonium pyrrolidone carboxylate commercially available from Amerchol...

...exclamation mark)ayer of the laminate to be position next to the backsheet, Alternatively the **chitosan** material can be sprayed on the first (inverted exclamation mark)ayer of the backsheet (also called secondary backsheet) and the laminate core is free of **chitosan**.

Figure 2 represents a sectional view of a pantiliner structure 100 of Example 2 which...

...AGM) is added between the two fissure layers of the laminate on top of the **chitosan** material. The AGM added is cross-linked sodium polyacrylate available from DOW Chemicals Germany under...Silica gel 123 or Syloblanc 82) at a basis weight of 61 g/m<sup>2</sup>.

A **chitosan** solution is sprayed on the air laid tissue layer of the laminate directed towards the backsheet. The **chitosan** solution is prepared by solubilizing 1 g of chitosonium pyrrolidone carboxylate commercially available from Amerchol ...are prepared similar to the ones in Examples 127 13 and 14 except that the **chitosan** solution is sprayed on the first layer of the backsheet (also called secondary backsheet) and the core laminate is free of **chitosan**.

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#### Claim

... absorbent core, said core being intermediate said topsheet and said backsheet, said article comprising a **chitosan** material.

2 An article according to claim 1 wherein the **chitosan** material has a degree of deacetylation of more than 75%, preferably from 80% to about...

...to

about 100%.

3 An article according to any of the preceding claims wherein the **chitosan** material is selected from the group consisting of **chitosans** , **chitosan** salts, crosslinked **chitosans** , modified **chitosans** and mixtures thereof.

4 An article according to any of the preceding claims wherein the **chitosan** material is a **chitosan** salt, typically a **chitosan** salt of citric acid, formic acid, acetic acid, N-acetylglycine, acetylsalicylic acid, fumaric acid, glycolic acid, iminodiacetic acid, itaconic acid, lactic acid, maleic acid, malic acid, **nicotinic acid** , salicylic acid, succinamic acid , succinic acid , **ascorbic acid** , aspartic acid , glutamic acid, glutaric acid, malonic acid, pyruvic acid, sulfonyldiacetic acid, benzoic acid, epoxysuccinic acid, adipic...

...gm-2 and most preferably from 4 gm-2 to 50 gffl-2 of a **chitosan** material or a mixture thereof.

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. An article according to any of the preceding claims...

...article such that the bodily fluid first contacts the absorbing gelling material before contacting the **chitosan** material.

9 An article according to claim 8 wherein the absorbent core comprises a tissue...

...layers, one facing the topsheet and one facing the backsheet, said tissue laminate comprising the **chitosan** material and absorbent gelling material disposed between said two tissue layers, wherein the **chitosan** material is directed towards the backsheet, preferably the **chitosan** material is applied onto the tissue (inverted exclamation mark)ayer facing the backsheet.

10 An...

...any one of the preceding claims, wherein said article is a sanitary napkin, a nursing pad , baby diaper or a panty liner.

19 The use of a **chitosan** material in a breathable absorbent article suitable for absorbing bodily fluid, comprising a (inverted...

15/3,K/12 (Item 12 from file: 349)  
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APPLICANT

01027585 \*\*Image available\*\*  
BANDAGE FOR ABSORBING EXUDATES COMPRISING POLY(ETHYLENEOXIDE)- AND  
CHITOSAN -BASED COMPOUNDS

PANSEMENT ABSORBANT L'EXSUDAT, COMPRENANT DES COMPOSES A BASE DE  
POLY(ETHYLENEOXYDE) ET CHITOSANE

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RU SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW  
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BANDAGE FOR ABSORBING EXUDATES COMPRISING POLY(ETHYLENEOXIDE)- AND  
CHITOSAN -BASED COMPOUNDS

PANSEMENT ABSORBANT L'EXSUDAT, COMPRENANT DES COMPOSES A BASE DE  
POLY(ETHYLENEOXYDE) ET CHITOSANE

Fulltext Availability:

Detailed Description

Claims

English Abstract

A bandage of the type used on acute wounds , minor wounds , burn wounds and irritations , includes a first layer for covering the wound site and an area around the wound site, with the first layer including a top surface and bottom surface; a second layer over the first layer bottom surface, for absorbing exudates from the wound site; the secondlayer including a poly(ethyleneoxide)-based compound and a chitosan -based compound. A third layer is situated over the second layer, the third layer being of a perforated film, and wherein, at least one antimicrobial agent is associated with the bandage in a position where the antimicrobial agent will come in contact with the wound site, and which is transferable from the bandage to the wound site, upon contact with the wound site.

17 The bandage of claim 15 wherein said wound healing antimicrobial agent is selected from niacinamide ascorbate and Chitosan niacinamide ascorbate.

18 The bandage of claim 15, wherein said wound healing antimicrobial agent is situated on the perforated anti-stick film layer.

19 A method of making a bandage for improved wound healing, which includes the steps of coating an elastomeric base sheet with a suitable skin -friendly adhesive, affixing a layer of absorbent containing releasable hemostatic, 20. The method of making a bandage as described in claim 19, further including, overlaying the absorbent layer with a perforated nonstick...

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APPLICATION

01027584 \*\*Image available\*\*

ADHESIVE BANDAGE CONTAINING AN ANTIMICROBIAL AND AN HEMOSTATIC AGENT  
PANSEMENT ADHESIF CONTENANT UN AGENT ANTIMICROBIEN ET UN AGENT HEMOSTATIQUE

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RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

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ADHESIVE BANDAGE CONTAINING AN ANTIMICROBIAL AND AN HEMOSTATIC AGENT

Fulltext Availability:

Detailed Description

Claims

English Abstract

An adhesive bandage of the type used on acute wounds , burn wounds , minor wounds , or irritations includes a first layer for covering the wound site and an area around the wound site. The first layer includes a top surface and bottom surface. A second adhesive layer is situated over the first layer bottom surface, for adhering the adhesive bandage to a wound site. A third absorbent layer is situated over the second layer, for absorbing exudates from the wound site. A fourth layer is situated over the third absorbent layer for allowing limited flow of exudates from the wound site to the third layer. At least one each of an antimicrobial agent and a hemostatic agent or a multifunctional wound healing agent are each associated with the adhesive bandage in a position where the agents will come in contact with the wound site.

French Abstract

...type utilise pour des plaies graves, des plaies de brulures, des plaies mineures ou des irritations . Ce pansement comprend une premiere couche destinee a recouvrir la plaie et la zone entourant...

Detailed Description

ADHESIVE BANDAGE CONTAINING AN ANTIMICROBIAL  
AND AN HEMOSTATIC AGENT

Field of the Invention

= (US) #2003/0125654

The present invention relates to bandages and dressings for use by consumers.

More particularly, the present invention relates to adhesive bandages and wound dressings for use by consumers, that promote wound healing , as well as methods of producing and using same.

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00813685

CHITOSAN BIOPOLYMER FOR THE TOPICAL DELIVERY OF ACTIVE AGENTS  
BIOPOLYMER DE CHITOSANE UTILISE DANS L'ADMINISTRATION PAR VOIE TOPIQUE  
D'AGENTS ACTIFS

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CHITOSAN BIOPOLYMER FOR THE TOPICAL DELIVERY OF ACTIVE AGENTS  
BIOPOLYMER DE CHITOSANE UTILISE DANS L'ADMINISTRATION PAR VOIE TOPIQUE  
D'AGENTS ACTIFS

Fulltext Availability:

Detailed Description

Claims

English Abstract

...a carrier base for the topical delivery of an active agent comprising  
a high viscosity chitosan biopolymer. The invention further relates to  
a method of controlling the release of an active agent from a carrier  
base, comprising as a carrier base a high viscosity chitosan ; providing  
the active agent; and mixing the active agent and the chitosan .

Preferably, the carrier base comprises a high viscosity chitosan having  
a molecular weight of at least about 100,000 Dalton, more preferably at  
least...

...Dalton and most preferably at least about 300,000 Dalton. In other  
preferred embodiments the chitosan has a concentration of at least  
about 2 weight %....

French Abstract

...utilisee dans l'administration par voie topique d'un agent actif  
comprenant un biopolymere de chitosane a viscosite elevee. L'invention  
concerne egalement une methode permettant de commander la liberation d'un  
agent actif d'une base de transport, comprenant comme base de transport  
un chitosane a viscosite elevee, consistant a generer l'agent actif, et  
a melanger l'agent actif et le chitosane . De preference, la base de  
transport comprend un chitosane a viscosite elevee possedant un poids  
moleculaire d'au moins 100 000 Dalton environ, preferablement...

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...preferablement d'au moins 300 000 Dalton environ. Dans d'autres modes de réalisation, le **chitosane** a une concentration d'au moins 2 % en poids environ.

#### Detailed Description

##### **CHITOSAN** BIOPOLYMER FOR THE TOPICAL DELIVERY OF ACTIVE AGENTS FIELD OF THE INVENTION

This invention relates to carrier bases for the topical delivery of active agents comprising high viscosity **chitosan** biopolymers. Preferred carrier bases comprise **chitosan** having a molecular weight of at least 250,000 Dalton. The invention also relates to carrier bases comprising high viscosity **chitosan** at a concentration of at least 2 weight%. The present invention further provides a delivery...

...with delivery systems for  
retinoids.

##### BACKGROUND OF THE INVENTION

A number of changes occur in **skin** tissue as a consequence of aging, photodamage, and diseases, e.g., **skin** cancer and acne. **Skin** connective tissue is comprised primarily of fibrillar collagen bundles and elastic fibers, along with 1...

...be largely a product of fibroblasts.

A number of changes occur in the structure of **skin** connective tissue as a consequence of aging or photodamage. Age-related changes include a decrease...

...2000). In addition, the HA in the epidermal extracellular matrix has disappeared completely in aged **skin** (Neudeker et al., 2000). These alterations are believed to be largely responsible for the thin, fragile, and finely wrinkled quality of naturally-aged **skin**. Photoaged **skin** is characterized by the presence of elastotic material and damage to the collagen bundles. Clinically, photoaged **skin** appears thick and rough, with coarse wrinkles and mottled pigmentation (Lavker, 1995).

The alterations in **skin** connective tissue in **skin** aging and photodamage and **skin** diseases seem to be mediated mainly by collagen which comprises the bulk of the connective...

...increased destruction seem to occur.

Collagen synthesis is reduced in both photoaged and naturally aged **skin** (Griffiths et al., 1993; Talwar et al., 1995; Varani et al., 2000). In vivo studies (1986; Mays et al., 1990; Furth, 1991) In photodamaged **skin** UV irradiation has been shown to increase production of matrix metalloproteinases (MMP) which destroy collagen...

...such as hyaluronan.

There are many known agents that are used for the treatment of **skin** diseases and defects, including, e.g., retinoids, vitamins, and alpha-hydroxy acids. Topical application of...

...retinol has been shown to stimulate collagen synthesis in naturally aged as well as photoaged **skin** (Varani et al., 2000; Griffiths et al., 1993). The active substance seems to be All...



...are related. Indirect evidence exists that retinol transforms into All-trans retinoic acid in human skin (Kang et al, 1995). Retinoids appear to affect the quantity of collagen by increasing the number of collagen-producing fibroblasts, increasing collagen synthesis and/or by reducing MMP levels in skin, thereby decreasing destruction of collagen (Varani et al., 2000). However, retinoids do not seem capable...

...the quality of the collagen being

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produced as evidenced by)io change in the dermal connective tissue abnormalities after retinoid treatment (Varani et al., 2000). For increasing the quality of...

...which play a role in tissue reorganization.

Although retinoid treatment induced measurable changes in the dermal fibroblast population, it did not alter age-associated connective tissue abnormalities such as correct collagen...

...altering

these abnormalities and reverse or minimize the effects of aging or photodamage on the skin.

Retinoids are also used to treat other skin conditions such as acne, actinic keratosis, psoriasis, skin cancers and have been found to useful therapeutic agents in the chemoprevention of melanoma (Stani...

...tumor progression has significant implications for melanoma chemoprevention.

The incidence of malignant melanoma of the skin, the most serious form of skin cancer, is increasing faster than that of any other cancer in the United States (Koh...in Australia (Hall et al., 1999).

While strategies for malignant melanoma have included (1) public health  
3  
interventions (Koh and Geller, 1998), (2) adjuvant therapies (Demierre and Koh, 1997) and (3...

...chemoprevention having been demonstrated in cancers of the head and neck, lung, cervix, ovaries and skin (Lotan, 1996; Sankaranarayanan and Mathew, 1996, Labrecque et al., 1999). Topical application of tretinoin (all...

...been shown to decrease melanocyte numbers and reduce melanocytic atypia in the treatment of photodamaged skin (Bhawan et al., 1996) and small pilot ...and 9-cis-RA.

In presently used topical delivery systems for agents used to treat skin ailments, one side effect is increased irritation. For example, compared to oral administration, topical delivery of retinoids increases the concentration of retinoids in the dermal compartment 10- to 100-fold (Lehman et al., 1988).

However, topical tretinoin (ATRA) induces irritation in 90% of patients (Gilchrest, 1997), and other side effects include patchy erythema, localized swelling, xerosis, and scaling. Irritation has been attributed, in part, by an overload of the tretinoin dependent pathways with non-physiological amounts of exogenous tretinoin in the skin. (Siegenthaler et al., 1994). This irritation may be the reason for discontinuation of treatment for close to 50% of patients (Stam-Posthuma et al., 1998). This high incidence of irritation, leading to poor compliance, can preclude its use.

The incorporation of drugs into polymeric...

...The possibility of other polymers, such as the synthetic polymers described above, to penetrate the skin and enter the systemic circulation has been suggested by the authors after careful radiolabeled analysis...a delivery system that utilizes a non-synthetic carrier which is biodegradable after penetrating the skin layers.

Thus, it would be desirable to have a controlled delivery vehicle for active agents used to treat skin ailments, which would prevent the irritation seen in present treatments. For example such a delivery system for retinoids would enable chronic use of topical retinoids for treating skin ailments, including for melanoma chemoprevention. A controlled delivery system could make tretinoin topical therapy...

...for melanoma in individuals with dysplastic nevi who are at high risk of developing melanoma.

Chitosan is a natural, biodegradable cationic polysaccharide derived by deacetylating chitin, a natural material extracted from fungi, the exoskeletons of shellfish and from algae and has previously been described as a promoter of bioadhesive characteristics. Modified chitins and chitosans have been administered to humans in the form of dressings for wounded soft tissues and for the controlled delivery of drugs (Muzzarelli et al, 1986; 1999; Muzzarelli...

...1995; Maekawa and Wada, 1990; Mita et al., 1989). For the purpose of soft tissue healing the most relevant characteristics of chitin-based biomaterials are their biodegradability, biocompatibility and similarity to hyaluronan, beside their capacity to release glucosamine and N- acetyl - glucosamine monomers and oligomers (Muzzarelli, 1999).

Chitosan is insoluble in neutral to alkaline water and thus, it has to be exposed to acidic conditions to render it soluble. Methods for solubilizing chitosan include the use of a slightly acid solution (pH<6) containing acidic acid, glycolic acid, lactic acid, or other alpha-hydroxy acids. Other methods include producing derivatives of chitosan which obviate the need for acids to solubilize chitosan. For example, U.S Patent No. 3,953,608 in Vanlerberghe and Sebag describes a method of making chitosan soluble in water at pH>7 by acylation of the chitosan using organic anhydrides. This patent describes the use of these derivatives mainly as film formers for

coloring of the skin, deodorizing products and making antispot products. United States Patent Nos.

4,929,722 and 4,946,870 describe the use of chitosan derivatives in delivery

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systems for the delivery of pharmaceutical or therapeutic compositions. Patent

No. 4,929,722 describes, in particular, the method of making a chitin or

chitosan salt or covalent derivative from highly crystalline, partially deacetylated chitin or chitosan. These ionic derivatives of chitosan called

chitosonium polymers and covalent chitosan derivatives have been made by

dispersing chitosan in an aqueous/solvent mixture. Patent No. 4,946,870 describes the use of these chitosonium polymers and covalent chitosan derivatives. U.S. patent No. 5,300,494 describes the same delivery system to deliver...

...may prevent the overload of retinoids into the systemic circulation, which may be responsible for irritation and allow chronic use of topical retinoids. In addition, it would be useful to have...

...a carrier base for the topical delivery of an active agent comprising a high viscosity chitosan biopolymer. Preferably, the carrier base comprises a high viscosity chitosan having a molecular weight of at least about 100,000 Dalton, more preferably at least...

...Dalton and most preferably at least about 300,000 Dalton. In other preferred embodiments the chitosan has a concentration of at least about 2 weight%. In an especially preferred embodiment, the carrier base comprises a high viscosity chitosan biopolymer having a molecular weight of at least about 300,000 Dalton and at a...

...pharmaceutical actives and therapeutic actives. Preferred pharmaceutical actives are those used for the treatment of skin diseases, e.g., retinoids, corticosteroids, non-steroidal antiinflammatory drugs (NSAIDS), hormones, anti-fungal agents, anti...

...the carrier, retinoids and alpha-hydroxy acid.

In certain compositions of the present invention the chitosan has a molecular weight of at least about 300,000 Daltons. In certain of these embodiments, the chitosan is present in a concentration greater than about 2%. These compositions are especially useful for the chitosan has a

molecular weight of about 10,000 to about 250,000 Dalton. In certain of these embodiments the chitosan is present in a concentration greater than about 5%, more preferably between about 5% up...

...comprising a carrier base and a retinoid, wherein the carrier base comprises a high viscosity chitosan. Preferably, the carrier base comprises a high viscosity chitosan having a molecular weight of at least about 100,000 Dalton, more preferably at least...

...Dalton and most preferably at least about 300,000 Dalton. In other preferred embodiments the chitosan has a concentration of at least about 2 weight%. In an especially preferred embodiment, the carrier base comprises a high viscosity chitosan biopolymer having a molecular weight of at least about 300,000 Dalton and at a...

...an active agent from a carrier base, comprising as a carrier base a high viscosity **chitosan** ; providing the active agent; and mixing the active agent and the **chitosan** . Preferably, the carrier base comprises a high viscosity **chitosan** having a molecular weight of at least about 100,000 Dalton, more preferably at least...

...Dalton and most preferably at least about 300,000 Dalton. In other preferred embodiments the **chitosan** has a concentration of at least about 2 weight % . In an especially preferred embodiment, the carrier base comprises a high viscosity **chitosan** biopolymer having a molecular weight of at least about 300,000 Dalton and at a...

...weight %.

In certain methods, the method further comprises the step of selecting a concentration of **chitosan** depending on the molecular weight of the **chitosan** provided so that a viscosity of at least about 100 cps is obtained.

In preferred...

...comprises a pharmaceutical active, e.g., an agent that is used for the treatment of **skin** diseases. Examples of pharmaceutical actives include, but are not limited to retinoids, such as corticosteroids...

...pharmaceutical active or a therapeutic active.

The invention also relates to a method of treating **skin** diseases providing to the diseased **skin** a composition containing a high viscosity **chitosan** biopolymer and an active agent. Preferably, the high viscosity **chitosan** has a molecular weight of at least about 100,000 Dalton, more preferably at least...

...Dalton and most preferably at least about 300,000 Dalton. In other preferred embodiments the **chitosan** has a concentration of at least about 10 weight % . In an especially preferred embodiment, the high viscosity **chitosan** biopolymer has a molecular weight of at least about 300,000 Dalton and at a concentration of at least 2 weight %.

Examples of **skin** diseases include, but are not limited to, acne, melanoma, premature **skin** aging, and photodamage. In preferred embodiments the active agent comprises a pharmaceutical active, e.g., an agent that is used for the treatment of **skin** diseases. Examples of pharmaceutical actives include, but are not limited to retinoids, such as corticosteroids...

...or a therapeutic active. In certain embodiments of the present invention, the methods of treating **skin** diseases comprises the compositions of the present invention, as described herein, in conjunction with other treatments for the disease. For example, in treating precancerous **skin** conditions, it may be useful to use the compositions of the present invention with standard...

...invention further relates to compositions for the topical delivery of an active agent comprising a **chitosan** biopolymer and the active agent,

wherein the  
  **chitosan** has a molecular weight of at least about 300,000 Daltons and  
  is  
  present at...

...the transdermal  
  delivery of the active agent.

In preferred compositions of the present invention, the **chitosan**  
  biopolymer comprises a **chitosan** having a molecular weight of at least  
  about 100, 000 dalton. Preferably the **chitosan** has a molecular weight  
  ranging from about 250,000 daltons to about 1000,000, more...

...from about 300,000 to about 800,000  
  Dalton.

1 1

In certain embodiments the **chitosan** has a molecular weight from about  
  300,000 to about 800,000, at a concentration of at least about 2%. In  
  other embodiments, the **chitosan** has a molecular weight from about  
  100,000 Daltons to about 300,000 and a...

...of at least about 5%.

In preferred methods and compositions of the present invention, the  
  **chitosan** has a degree of deacetylation of from about 70% to about 90%.

In preferred embodiments...BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph that shows ATRA distribution with **chitosan** topical  
  delivery.

Figure 2 shows the use of high molecular weight (HMW) **chitosan** to  
  enhance transdermal delivery.

Figure 3 shows ATRA distribution using 3% HMW **chitosan** .

Figure 4 is a graph showing ATRA permeation with the high molecular  
  weight **chitosan** (TD012).

Figure 5 is a graph that shows ATRA permeation of the high molecular  
  weight **chitosan** and middle molecular weight **chitosan** (TM76 1).

Figure 6 shows the stability of ATRA gels of the present invention at...

...of the present invention at 400C.

Figure 8 shows the stability of ATRA in HMW **chitosan** .

Figure 9 is a graph that shows that as the **chitosan** concentration  
  increases from 1% to 3% this results in a more gradual release of  
  retinoic acid from the **chitosan** matrix.

DETAILED DESCRIPTION OF THE INVENTION

The methods of the present invention provide a system...

...reduction of drug toxicity. More particularly, the present invention  
  relates to the use of a **chitosan** carrier for the topical delivery of an  
  active agent, e.g., retinoids, where the sustained release of the drug  
  can be altered by varying the properties of the **chitosan** that is used  
  as a carrier base for the drug.

As used herein, the term...

...actives include, but are not limited to, agents that are used for the treatment of skin diseases, e.g., retinoids, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDS), hormones, anti-viral agents...

...within the body, or alters the cosmetic appearance of the tissue of interest, e.g., skin, but is not technically considered a drug. Examples of therapeutic actives include, but are not...in that art and includes the application of the compounds of the present invention to skin surfaces, including mucosal surfaces, such as labial, rectal and genital mucosal surfaces.

The term "carrier...

...of the active agent that is being delivered. Preferred carrier bases comprise a high viscosity chitosan having a molecular weight of at least about 100,000 Dalton, more preferably at least...

...Dalton and most preferably at least about 300,000 Dalton. In other preferred embodiments the chitosan has a concentration of at least about 2 weight %. In an especially preferred embodiment, the carrier bases comprises a high viscosity chitosan biopolymer having a molecular weight of at least about 300,000 Dalton and at a concentration of at least 2 weight%.

The term "high viscosity" chitosan refers to a chitosan biopolymer having a viscosity of at least about 100 cps. The viscosity of the chitosan solution can readily be determined by one of ordinary skill in the art, e.g., by the methods described in Li et al., Rheological Properties of aqueous suspensions of chitin crystallites. J Colloid Interface Sc 183:365-373, 1996. In addition, viscosity can be estimated ...

...a fraction (Form No. 198 997GW, Dow Chemical Company). In certain embodiments, the high viscosity chitosan preferably has a viscosity greater than at least 100 cps, and more preferably greater than at least 500 cps. The term "low viscosity" chitosan refers to a chitosan solution having a viscosity of at least about 1-30 cps. "Middle viscosity" refers to a chitosan having a viscosity of about 30-100 cps. Viscosity measurements reported here refer to a chitosan solution at 1% concentration in 1% acetic acid measured in a Brookfield LVT viscometer with...

...high concentration" as used herein, may refer to a concentration of greater than about 2% chitosan in the solution. The term "low concentration" refers to up to about 1% chitosan. The term "middle 14 concentration" refers to between about 1 and about 2%.

The term "high molecular weight" chitosan, also referred to herein as HMW, refers to chitosan having a molecular weight of at least about 250,000 Dalton. The term "middle molecular weight" chitosan, also referred to herein as MMW, refers to chitosan having a molecular weight of at least about 50,000 up to about 250,000 Dalton. The term "low molecular weight" chitosan, also referred to herein as LMW, refers to chitosan having a molecular weight

up to about 50,000 Dalton. In preferred embodiments, the carrier base is a **chitosan** having a molecular weight of at least about 250,000 Dalton, more preferably at least...

...present invention rely on the discovery of the inventors that the desired viscosity of the **chitosans** can be achieved by manipulating the concentration, i.e., percentage, of different molecular weight **chitosans**. For example, as shown in Table 1, a viscosity of greater than 100,000 cps can be obtained by using 12% of a LMW **chitosan**, 5% of a MMW **chitosan** or 3% of a HMW **chitosan**.

Table 1. Viscosity-concentration relationship for different viscosity-grade **Chitosans**

LMW	MMW	HMW
Viscosity %	Viscosity %	Viscosity %
(cps)	(cps)	(cps)
1	66	1
552	1	21...

...the active agent by varying the concentration, molecular weight and, therefore the viscosity of the **chitosan**. For example, in one embodiment of the present invention, the use of a greater concentration of a lower molecular weight **chitosan** will provide similar release rates as a higher molecular weight **chitosan**.

Retinoids, e.g., retinoic acid, are hydrophobic and highly insoluble. We have found that delivery...

...base. Thus, we have found that the higher the viscosity of the colloidal solution of **chitosan**, the slower the release of the agent being

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delivered. For example, the retinoids in the present compositions are released

as the polymer film on the **skin** surface becomes hydrated. As the film containing the drug and carrier dissolves away, new layers...

...are exposed, leading to further release of the drug to the affected area of the **skin**.

The inventors have found that the **chitosan**-based controlled delivery system of the present invention for delivery of retinoids enhances the transdermal...

...where warranted, yet prevents the overload that results from traditional retinoid treatments and thus reduce **skin irritation**.

As discussed further below, experiments using Franz diffusion cells have shown that carrier bases of the drugs, as desired.

The cumulative All-Trans-Retinoic Acid (ATRA) levels in each **skin** compartment of hairless mouse **skin** after about 200 hrs exposure to different **chitosan** formulations is shown in Figure 1. By varying the viscosity of the

**chitosan** from 550 cps for the 1% High Molecular Weight (HMW) **chitosan** (MW-360,000 Dalton) to an estimated 3.27 million cps for the 8% Middle Molecular Weight (MMW) **chitosan** (MW-120,000 Dalton) it is possible to obtain 'de range of retinoid distributions. The cumulative percutaneous penetration

a WI 1 1

across the **skin** is inversely proportional to the amount of retinoid remaining on the **skin** surface. As the amount of retinoid remaining on

the skin surface decreases from around 90% of the applied dose for the 8% MMW chitosan to less than 30% for the 1% HMW, the percutaneous penetration of retinoid increases from less than 10% to around 70%. Likewise, the amount of retinoids in the skin layers increases from less than 1% for the 8% MMW to around 5% for the 1% HMW.

Figure 2 shows the 1% HMW chitosan, containing 0.1% ATRA compared to a control gel, containing 0.1 g ATRA. The 1% HMW chitosan contains 0.1% ATRA (0.1 g ATRA, 0.04 g butylated hydroxytoluene (BHT), 1 g of Cremophor® RH40, 15 g ethanol (200 proof), 1 g of Chitosan HMW, 81.8 g water, 1 g of glacial acetic acid]. The control gel contained...

...the HMW formulation compared to around 45% with the control gel formulation. A 1% HMW chitosan formulation can be used to enhance the transdermal penetration of retinoids to maximize the therapeutic power of retinoids.

Figure 3 shows that the 3% HMW chitosan [containing 0.1% ATRA (0.1 g ATRA, 0.04 g butylated hydroxytoluene (BHT), 1 g of Cremophor® RH40, 15 g ethanol (200 proof), 3 g of Chitosan HMW TDO 12, 80.8 g water, 1 g of glacial acetic acid] compared to...

...with the HMW formulation compared to 45% with the control gel formulation. A 3% HMW chitosan formulation could be used to control release the retinoids and limit the potential for irritation.

Figure 4 shows the ability to release ATRA from the chitosan formulations is highly dependent on their viscosity which range from 552 cps for 1% HMW...

...formulations ranging from 1% to 3% HMW.

In Figure 5, the percutaneous permeation of MMW chitosan gels of high viscosity (viscosity of 3.27 million cps for the 8% MMW estimated...

...estimated viscosity of 17,163 cps). The topical ATRA formulations containing the higher viscosity chitosan display a lower percutaneous penetration through hairless mouse skin  
17  
after 220 hours of continuous application in a Franz cell apparatus.

One of ordinary skill in the art can readily select an appropriate chitosan component as the carrier for the compositions and methods of the present invention, based upon...

...equation for predicting release rates from polymer concentrations and viscosities. As aforesaid, a lower viscosity chitosan used at higher concentrations will provide similar release rates as a higher viscosity chitosan. Thus, if it is desirable to have a slow release of the retinoids, one would select a carrier base having a high viscosity chitosan, e.g., a chitosan with molecular weight of at least about 100,000 Dalton, e.g., 300,000, at...

...type of composition is desirable to minimize the overload of retinoids



which may lead to irritation of the skin .

Alternatively, if it is desirable to have a faster release of the retinoid, one would select a chitosan solution having a high molecular weight, e.g., of at least about 250,000, at...

...transdermal release of the active agent over a shorter period of time.

The combination of chitosan and retinoids in the compositions of the present invention enhances the normal tissue architecture of naturally and photoaged skin while reducing skin irritation , normally seen with retinoid preparations.

The compositions of the present invention can be formulated into...cis and trans), alpha-tocopherol (Vitamin E), 7-dehydrocholesterol (Vitamin D), Vitamin K, thiamine riboflavin, niacin , pyridoxine, biotin, pantothenic acid , ascorbic acid , choline, inositol, and the like. Antiinflammatory corticosteroids such as progesterone, hydrocortisone, prednisone,  
19  
fludrocortisone, triamcinolone...

...lactic acid, singularly or in combination with anti-viral agents. Anti-alopecia agents such as niacin , nicotinate esters and salts, and minoxidil. Sun-Protective agents such as aminobenzoates, Para-aminobenzoic acid (PABA...aerosols, solutions, may also be included.

Alternatively, solutions or mixtures of the actives with the chitosan derivatives may be prepared with or without some of the adjuvant ingredients, and these solutions...

...films, rods, sheets, sponges or fibers for use as suppositories, medicated sutures, medicated sheets, medicated bandages , patches , and the like. It is relatively easy to process chitosan into various forms such as small particles, gel, and cotton mesh for drug delivery applications...

...art.

In a preferred composition, alpha-hydroxy acid (AHA) is used to completely dissolve the chitosan . AHA is also referred to as glycolic acid in the methods and examples described below...

...using alpha -hydroxy 'd 'stwo-fold. One advantage is that it helps dissolve the chitosan . Another

aci 1 1

advantage is that the combination of alpha-hydroxy acid and chitosan , which is basic, raises the pH of the composition which in turn, minimizes the peeling hydroxy acids may prevent hyaluronan (HA) enhancement (Neudecker et al., 2000). Chitosan , through the presence of its amino groups on the polymer chain, can be used to neutralize the alpha hydroxy acids. The addition of 3% HMW chitosan raises

2 1

the pH of an alpha hydroxy solution from 3.5 to 5...

...effect the ability to stimulate HA production rather than implement their action by peeling the skin and cause diffuse wound healing .

AHA is thus useful as an active agent alone, or in conjunction with

another pharmaceutical...

...invention are stable, as is necessary for topical treatments. ATRA gels made from the HMW **chitosan** at concentrations greater than 2% are stable for at least 120 days and comparable in...

...the standard control gels made from Carbopol as shown in Figure 6. Lower concentrations of **chitosan** may cause a reduction in the stability of the ATRA in the gel formulation. As...

...are highly stable, again as a result if the high viscosity of this type of **chitosan** when present at greater than 2% concentration. Similar results would be obtained with the MMW **chitosan** present at concentration than 5% w/w. The difference in stability is related to the ...

...The inventors have found that the use of a carrier base with a highviscosity grade **chitosan**, e.g., having a molecular weight of at least about 300,000 Dalton and at...

...Figure 8 and Example 3, below. Thus, one advantage of using a high molecular weight **chitosan** in delivering an active agent, such as retinoids, is the ability to use a lower...

...a period of several months.

To the best of our knowledge there are presently no **chitosan**-based retinoid delivery systems. For percutaneous drug delivery **chitosan** offers unique advantages. For example, **chitosan** is used in cosmetology to make moisturizing creams. The concentration in moisturizers and soaps varies from 0.3% to 1% **chitosan**. These concentrations have been experimentally tested by the manufacturers and are well tolerated on the **skin**. It is also used in hair sprays, styling gels and shampoos: its cationic nature enables a close bond to

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the keratin anion (Sachetto, 1986; Cleenewerck, 1994). **Chitosan** is a biodegradable polymer which has advantages over a synthetic polymer, e.g., PP2. For example, **chitosan** is completely degraded in the body. It degrades without leaving residual matter which could build up in the tissues. As suture material, **chitosan** has been shown to be completely absorbed in one to two months so it would release the drug during the same period (Suzuki, 1995). It is unnecessary to remove **chitosan** from the body after the complete release of the drug because **chitosan** has good biodegradability and is completely dissolved by enzymes such as lysozyme. As aforesaid, the present invention provides methods for the treatment of many **skin** ailments. To our knowledge there is no controlled topical delivery system of retinoids for melanoma chemoprevention. One aspect of the present invention is a **chitosan** based percutaneous delivery system for the chemoprevention of melanoma in individuals with dysplastic nevi who are at high risk of developing melanoma.

In addition, the combination of retinoids and a **chitosan**-based delivery system takes advantage of the immunostimulating properties of **chitosan** for the delivery of therapeutic actives in **skin** conditions that necessitate an immune response. The compositions of the present invention utilize the property of **chitosan** to initiate immune and reparative functions, either directly or

indirectly through the stimulation of macrophages in the skin tissue.

Activation and production of cytokines such as IL- 1 leads to increased angiogenesis and skin reparative functions. IL- 1 and TNF-  $\alpha$ , produced by macrophages, stimulate fibroblasts (Chang J et al. 1986). Chitosan has been shown to stimulate macrophage production, resulting in activation of cytokines such as interleukin...

...the reduction of immunostimulatory activity (Nishimura et al, 1984, 1985, 1986, 1990). A 70% deacetylated chitin has been used in combination with petrolatum to immunostimulate the skin in the management of senile erythroderma. (Horuchi & Otoyama, 1996). The chitin derivative is not employed in these studies as a delivery system but rather as the...

...23  
ingredient in the topical petrolatum-based formulation.

In addition, the chito-oligomers released from chitosan by the in vivo hydrolytic action of lysozyme and N- acetyl -p-D- glucosaminidase after penetration of chitosan into the skin may stimulate hyaluronan synthesis.

Recent evidence is found for the presence of DG42 protein (a...

...mouse cells leads to the synthesis of chito-oligomers, and hyaluronan synthase preparations also contain chitin synthase activities (Varki A, 1996; Semino et al., 1996; Bakkers et al., 1997).

Chitosan has the potential, directly or indirectly through the formation of hyaluronic acid, to correct this...

...fiber thinness, fiber disorganization and depth of disorganization.

Therefore the administration of retinoids via a chitosan carrier base has the potential of enhancing both the quantity and quality of new collagen production in skin connective tissue.

The methods of the present invention take advantage of the reparatory effect of chitosan to stimulate fibroblasts in ...products as well as for products that are used to treat photodamage and other such skin conditions.

As aforesaid, the compositions of the present invention are useful for treating skin diseases. Examples of skin diseases which can be treated include, but are not limited to, acne, melanoma, premature skin aging, and photodamage. In preferred embodiments the active agent comprises a pharmaceutical active, e.g., an agent that is used for the treatment of skin diseases. Examples of pharmaceutical actives include, but are not limited to retinoids, such as corticosteroids...

...amount of agent present in the system.

As aforesaid, in some methods of treating certain skin diseases, it may be useful to use the compositions of the present invention in conjunction with other treatments for the disease. For example, in treating precancerous skin conditions, it may be useful to use the compositions of the present invention with standard...

...the topical delivery system different polymer formulations were prepared. Table 2 shows the types of **chitosan** used. The **chitosan** was obtained from Primex Ingredients, Avaldnes, Nor-way.

These formulations were then tested in in...

...cell. Human subjects are then exposed to selected formulations (in vivo) and compared to current **dermal** retinoid formulation to test their ability to reduce irritation .

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Table 2

TYPE OF VISCOSITY1 DEGREE OF

**CHITOSAN** (MPAS) DEACETYLATION2 DESCRIPTION  
(LOT)

Soluble in 1% Acetic Acid

HMW 552 89.0% or 2...the following examples, sample TDO 12 is an example of a high

molecular weight (HMW) **chitosan** , TM761 is an example of a middle molecular

weight (MMW) **chitosan** , and TM6 1 5, TM816 and TM611 are examples of low molecular weight (LMW) **chitosans** .

EXAMPLE 1: Preparation of **chitosan** -retinoid compositions

Gel **Chitosan** TDO 12 has a viscosity of 500 cP when dissolved with 1 % glacial acetic acid...

...estimated 171,163 cps at 3%

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concentration.

Colloidal solutions up to 3% (wt/wt) **chitosan** were obtained by dissolving high molecular weight chitosLui (HMW (TDO 12); MW 360,000 Daltons...

...glacial acetic acid at room temperature. Carrier bases up to 8% were obtained by suspending **chitosan** powder of middle molecular weight (MMW (TM76 1); MW 120,000) (8 g in 66...

...and adding 25 g of water and 1 g of glacial acetic acid, dropwise to **chitosan** to form a clear, highly viscous solution after cooling at room temperature.

EXAMPLE 2 - In vitro **skin** penetration studies using radiolabeled retinoids.

Fresh hairless mouse **skin** samples were obtained from surgery, and upon arrival to the lab they were stored in a freezer (-20 'C). Immediately prior to the permeation experiments, **skin** samples without subcutaneous fat were thawed by floating on water at 22 'C for about 10-20 minutes. A 1.0 CM<sup>2</sup> portion of the **skin** samples was fastened between the Franz diffusion cell's receptor chamber and chimney top by...

...castor oil (cremophor

RH40, BASF Corporation) and were mixed with 8.5 grams of the **chitosan** colloidal solution.

For the cream sample preparation, 20 uL of radiolabeled 3H-Retinoic Acid (20...I g of Seabuckthorn Seed Extract.

Finally, 7.8 g of TDO 12 (2.9%) **chitosan** , dissolved in glycolic acid (pH S. 5) was added homogeneously.

Approximately 200 mg of each formulation was applied to the sample compartment (i.e. the epidermal side) of the **skin** sample. The **dermal** surface of

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the **skin** was perfused with receptor phase solution (phosphate buffered saline containing 0.5% Volpo surfactant (Croda...

...vial with 10 ml of scintillation fluid. Any retinoid remaining on the surface of the **skin** (top wash) was extracted with 2 x 500  $\mu$ L of ethanol containing 1% glacial acetic...

...placed in a scintillation vial containing 9 ml of scintillation fluid (Packard).

The epidermis and **dermis** were digested overnight in 4 ml of tissue solubilizer (Solvable Tissue and Gel Solubilizer -Packard...

...analyzed by scintillation counting.

The permeation of all-trans retinoic acid (ATRA) across hairless mouse **skin** as a function of concentration of the high viscosity **chitosan** TDO 12 and middle viscosity TM761 is shown in figure 1. As shown in Figure...

...to increase the percutaneous penetration from 8% to 68% ATRA percutaneous penetration by changing the **chitosan** polymer from 8% TM761 (the medium viscosity **chitosan** : 10 cP at 1% concentration) to 1% TDO12 (high viscosity **chitosan**: 552 cP at 1...

...the amount of ATRA penetrating increases, there is a concomitant decrease of ATRA on the **skin** surface. The amount in the **skin** layers decreases from 5% to 0.5% as the amount of ATRA penetrated decreases. As the concentration of the high viscosity **chitosan** (TDO 12) decreases, the amount of ATRA permeated through the **skin** into the Franz Cell Reservoir compartment increases as shown in Figure 4. The ATRA release...

...CarbopoITM 940 NF acrylate polymer (BF Goodrich) is intermediary between the 1% and the 2% **chitosan** TDO 12.

These results show that it is possible to control the delivery of the retinoid ATRA by changing the **chitosan** concentration, in relation to the viscosity of the **chitosan** . An increase in concentration of the middle viscosity **chitosan** TM761 further reduces the permeation rate (Figure 5).

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EXAMPLE 3 - Stability Testing of retinoid gels and creams

A. Preparation of gels and creams based on retinoic acid and **chitosan** TDO 12.

For the preparation of gels and creams the high molecular weight TDO 12 **chitosan** (M.Wt 360,000 Dalton) was chosen due its slow release

characteristics for retinoic acid. We chose to use the TD012 Chitosan (2.9%) because it forms a highly viscous colloidal solution at room temperature and it...

...ATRA release profile.

0

Preparation of retinoic acid gel.

Solution A was prepared by dissolving chitosan in a 1% glacial acetic acid solution as follows: 2.9% Chitosan TD012, 79.98%Water in 1% Acetic Acid.

Solution B was prepared by dissolving cremophor...

...a 3-blade laboratory mixer.

Preparation of Retinol Cream was as follows.

Solution A: 3% Chitosan TD0 12  
appx. 62.84%Water  
2.86% Glycolic Acid (70% solution)  
appx. 3.5...

...100 ml) was added dropwise to raise the pH from 2.12 to 3 Then chitosan was added and allowed to dissolve completely overnight. The final pH was 5.5 Solution...

...solution was then stirred using a magnetic stirring bar and plate until the retinoid and chitosan had dissolved.

For the retinoic acid sample, a 100 @tL quantity was diluted 10-fold... sample 2 1 is the same as 2 1 without the Cremophor component.

#### EXAMPLE 4 - Patch Testing in Healthy Individuals

Human studies are undertaken to evaluate the irritation potential of the

chitosan /ATRA percutaneous delivery system. 15 patients having signed an

informed consent are patch tested with commercial creams containing 30

conventional ATRA and wit"Ia cream of the present invention containing chitosan and retinoids at a-i equivalent dose. The creams are prepared according to the methods in Example 3 and as shown below. The irritant potential of the tretinoin/ chitosan delivery system on human skin is assessed by means of patch test evaluations as follows.

For assessing irritation (Seaton, 1995), the occlusive Hill Top Chamber patch testing system (Hill Top Research, Inc., Cincinnati, Ohio) incorporates 0.2 ml of sample.

The...

...tretinoin (ATRA) cream (0. 0 1%, 0. 05% and 0. 1 %) with two concentrations of chitosan (1% and 3%) in the formulation.

The data is evaluated in terms of a Mean Irritation Score by evaluating the extent of erythema, as previously described (Mills and Berger, 1998).

Statistical evaluation includes both frequency and severity of erythema seen at sites treated with tretinoin containing **chitosan** and commercially available tretinoin using analysis of variance (ANOVA) and the paired t-test.

**Patch** testing of ATRA Cream

The drug product (ATRA Cream) consists of a modified retinoic acid...

## Part II

Given that the results of Part I show no irritation from the volar application of the formulations, Part II involves 3 additional human subjects, each subject receiving 3 patches containing 0.2 grams of test sample to the paraspinal area of the back to verify any irritation caused by the base alone without ATRA. The patch application is for 24 hours with irritancy evaluation at 30 minutes after patch removal and 24 hours after patch removal.

For Patients 7 to 9 Formulation (A, C as referred above)

Site 1 A (Base Cream)

Site 2 C (HMW- Chitosan 1%)

Site 3 C (HMW- Chitosan 3%)

The location of each test sample is rotated for each individual according to latin...irritancy, Part III involves the testing of 6 additional human subjects. Each participant receives 6 patches applied to the paraspinal area on the back, including 3 patches of the control cream and 3 patches of the 3.9% HMW- chitosan cream each containing 3 strengths of ATRA. Patches are removed after 24 hours and irritancy scored 30 minutes and 24 hours. Statistical evaluation...

...0.05% ATRA)

Site 3 B (Control Cream + 0.1 % ATRA)

Site 4 D (3% HMW- Chitosan + 0.01% ATRA)

Site 5 D (3% HMW- Chitosan + 0.05% ATRA)

Site 6 D (3% HMW- Chitosan + 0.15% ATRA)

The location of each test sample is rotated for each individual according to latin square design.

## EXAMPLE 5. CHITOSAN GELS AS DELIVERY VEHICLES FOR RETINOIC ACID

The topical carrier base consisting of high viscosity chitosan with a 34 molecular weight of at least 300,000 Dalton and at a concentration...

...the release of retinoic acid (RA).

Studies with [3H]retinoic acid. A high molecular weight chitosan (viscosity of 552 cP with 1% solutions in 1% acetic acid measured on a Brookfield...

...at 25 C, appropriate spindle at 30 rpm, Mwt of 360,000 Dalton). As the chitosan concentration increases from 1% to 3% this results in a more gradual release of retinoic acid from the chitosan matrix as shown in Figure 4.

EXAMPLE 6 - Preliminary in vitro evaluation of topical chitosan delivery system for retinoids,

A. Skin sample preparation.

Fresh skin (female abdominal) was obtained from surgery, and upon arrival to the lab was washed and...

...M phosphate-buffered saline (PBS) buffer (pH 7.4).

Subcutaneous fat was removed and the skin was rinsed in PBS, it was then dried and stored in the freezer (-20 C).

Prior to skin splittig, full skin was thawed overnight in sterile PBS. The split skin procedure consisted of taking a 4 x 4 cm full skin sample



and  
immersing it in water at 60 °C for approximately 60 sec. The epidermis...

...placed on aluminum foil and stored at -20 °C. Prior to the permeation experiment, split skin samples were thawed by floatation in water at 22 °C for - 20-40 minutes.

#### B. Vehicle Preparation

3.5% HMW- Chitosan (88.8% deacylated chitosan, 1000 cps viscosity, 800,000 MWt; Primex Ingredients SA, Avaldsnes, Norway) was dissolved in 1% acetic acid for 24 hours prior to mixing. The retinoid/ chitosan formulation was made up by adding concentrations of retinoids (ATRA or 9-cis-RA) ranging 1.75% HMW- chitosan

#### C. Franz diffusion cell setup

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All experiments used 9 mm amberized Franz diffusion cells...

...the receptor compartment and hence a more homogeneous distribution of the permeant (retinoic acid). Split skin (epidermis) samples of approximately 2.5 CM<sup>2</sup> surface area were carefully placed upon the receptor compartment ( dermis side facing down). The donor cap was then placed upon the skin and carefully clamped into place with a horseshoe clamp.

Receptor fluid (consisting of 25% ethanol...

...R = retinoid (@Lg) (from UV reading and standard curve), 25 = dilution factor; A= Area of skin exposed to formulation in sample compartment (0.785 CM<sup>2</sup>).

#### E. Preliminary Radiolabeled ATRA percutaneous studies

Retinoid penetration through human skin was determined as follows.

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@tl of 3H-ATRA (NET- 1 1 17) were mixed...

...2 g Cremophor RH-40, 1.0 g Vitamin E acetate, 50 ml 2.5% Chitosan (high MW Primex Superior). For the ethanol solution, the chitosan was omitted in the formulation.

200 @tl of this solution was then placed on the skin section within the Franz cell. A surface wash was performed at 24 hrs. The skin was washed and blotted and all IVR59 solution, washes and blots placed together in scintillation

fluid. The cleaned skin was then dissolved OIN in Soluene 350 and Sml scintillation fluid was then added to Aquasol-11). All scintillation solutions (top wash, skin and reservoir) were diluted 1: 1 000 and the radioactivity levels in these samples were counted.

#### F. Preliminary in vitro toxicity and irritation studies

The EpiDerMTM Skin Model (Epi-200, MatTek Corporation, Ashland, MA) is used to obtain in vitro skin toxicity MTT and IL- lot measurements indicative

of skin irritation as follows: Individual human equivalent cultures are transferred to six-well culture plates, each well...

...early embryogenesis of cyprinid fish. Proc Natl Acad Sci USA  
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#### Claim

... A carrier base for the topical delivery of an active agent comprising a high viscosity chitosan biopolymer.

2 The carrier base according to claim 1, wherein the chitosan has a molecular weight of at least about 100,000 Dalton.

3 The carrier base according to claim 1, wherein the chitosan has a concentration of at least about 2 weight% .

4 A composition for the topical...

...composition according to claim 5, wherein the pharmaceutical active is used for the treatment of skin diseases.

7 The composition according to claim 6, wherein the pharmaceutical active is selected from...

...at least

one additional active agent.

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. The composition according to claim 4, wherein the chitosan has a molecular weight of at least about 100,000 Daltons.

12 The composition according to claim I 1, wherein the chitosan is present in a concentration of up to about 3%.

13 The composition according to claim 4, wherein the chitosan has a molecular weight of about 10,000 to about 250,000 Daltons.

14 The composition according to claim 13, wherein the chitosan is present in a concentration of up to about 8%.

1 S. A composition for...

...a

carrier base and a retinoid, wherein the carrier base comprises a high viscosity 5 chitosan biopolymer.

16 The composition according to claim 15, wherein the chitosan biopolymer has a molecular weight of at least 100,000 Dalton and at a concentration...

...an active agent from a

carrier, comprising:

providing as a carrier base a high viscosity chitosan biopolymer;

providing the active agent; and

mixing the active agent and the chitosan .

21 The method according to claim 20, wherein the **chitosan**

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biopolymer has a molecular weight of at least 100,000 Dalton and at a...

...method according to claim 22, wherein the pharmaceutical  
active is used for the treatment of **skin** diseases.

24 The method according to claim 22, wherein the pharmaceutical  
active is selected from...wherein the therapeutic active  
comprises vitamins and alpha-hydroxy acids.

27 A method of treating **skin** diseases comprising providing to the  
diseased **skin** a carrier base containing a high viscosity **chitosan**  
biopolymer and an active agent.

28 The method according to claim 27, wherein the **chitosan** has a  
molecular weight of at least 100,000 Dalton.

29 The method according to claim 27, wherein the **chitosan** is at a  
concentration of at least 2 weight%.

30 The method according to claim 27, wherein the **skin** disease  
comprises acne, melanoma, premature aging, photodamage.

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. The method of treating **skin** diseases according to claim 27,  
further providing an anti-cancer drug.

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15/3,K/17 (Item 17 from file: 349)  
DIALOG(R)File 349:PCT FULLTEXT  
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**A METHOD FOR PROMOTING TISSUE REPAIR**

**PROCEDE VISANT A PROMOUVOIR LA REPARATION TISSULAIRE**

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Detailed Description  
Claims

**Detailed Description**

... the skin is the outer (epithelial) layer and the deeper connective tissue layer of the skin is called the dermis. The skin may have a thick or a thin epidermis and is therefore often classified as thick or thin skin. In the present context, the term " skin " embraces thick skin as well as thin skin.

Thick skin is found on the palms of the hands and the soles of the feet, whereas thin skin covers the remainder of the body. The skin on the palms of the hands and the soles of the feet has a thick epidermis with a particularly thick layer of keratin on its outer surface. The skin covering the remainder of the body has a relatively thin epidermis and the outer keratinized layer of the epidermis is relatively thin,

The skin forms a barrier between the body and the environment and one of the most important functions is to protect the body from invasion by potentially hazardous materials and organisms.

The skin consists of two layers of completely different kinds of tissue that are attached to one...

...it must be nourished via tissue fluid from a second and deeper layer of the skin. This second layer contains irregularly arranged connective tissue containing blood vessels. The outermost layer of the skin is the so-called stratum corneum. Then there is a viable layer called the



epidermis and the papillary dermis layer.

The epidermis and particularly its layer of keratin is a barrier to disease organisms...

...possible to have a bath without swelling or shrinking of the  
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**skin** . The epidermis contains cells producing melanin and is therefore able to protect the body from harmful effects of e.g. ultraviolet light. Furthermore, the **skin** serves as a temperature regulator and contains nerve endings responsible for picking up stimuli that...

...kinds of sensation during consciousness (e.g. touch, pressure, heat, cold and pain).

Hence the **skin** is of great importance in permitting man to adjust to his environment.

Since the **skin** is the most exposed part of the body, it is particularly susceptible to various kinds of **injuries** such as, e.g., ruptures, cuts, **abrasions** , **burns** and frostbites or **injuries** arising from various diseases. Furthermore, much **skin** is often destroyed in accidents. However, due to the important barrier and physiologic function of the **skin** , the integrity of the **skin** is important to the well-being of the individual, and any breach or rupture represents...

...must be met by the body in order to protect its continued existence.

Apart from **injuries** on the **skin** , **injuries** may also be present in all kinds of tissues and **injuries** like abscesses and internal ulcers are also treatable with a combination according to the invention. These **injuries** can have a wide range of severity and can have numerous internal as well as external causes. Probably the most frequent tissue injury is skin wounds due to simple external **trauma** . A tissue **injury** on a body surface caused by a disease is typically called an ulcer irrespective of its presence on the **skin** , in the gastrointestinal tract on any other mucosal surface (cf. below).

A tissue **injury** starts a cascade of reactions aimed at minimising the **injury** and preparing for tissue repair. Dependent on the type of tissue involved and the nature of the **injury** , different processes are more or less prominent. A process that aims at minimizing the **injury** is typically an inflammatory reaction, which even to some extent by itself can cause tissue **injury** . The transition from an inflammatory process to a tissue repair process is gradual and both...

...occur at the same time. The tissue repair process will only start if the tissue **injury** process is successfully stopped either by a physiologic process alone or in combination with a...

...For instance in crural leg ulcers a certain minimal blood supply is required for the **healing** process to be possible. When these conditions are met, the tissue repair process can start...

...and that is the formation of a transient connective tissue in the area of tissue **injury** . This process starts by forming a new extracellular collagen matrix by fibroblast. This new extracellular collagen matrix is then the support for a connective tissue during the final **healing** process. The final **healing** is in most tissues a scar formation containing connective tissue. In tissues which have regenerative properties, such as, e.g., **skin** and bone, the final **healing** includes

regeneration of the original  
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tissue. This regenerated tissue has frequently also some scar characteristics, e.g. a thickening of a healed bone fracture.

As almost all tissue repair processes include the early connective tissue formation, a stimulation of this and the subsequent processes are contemplated to improve tissue healing. In principle all tissue repair can benefit from a stimulation but the clinical impact of a stimulation of tissue healing will differ depending on the type of tissue injury and the subsequent healing process.

The value of a tissue healing stimulation is larger in conditions where the healing time is prolonged. A clinically important example of such a condition is leg ulcers.

In...

...restore the integrity of the skin barrier. The repair process for even minor ruptures or wounds may take a period of time extending from hours and days to weeks. However, in ulceration, the healing may persist for extended period of time, i.e. months or even years. Thus, failure to heal of cutaneous ulcers is a serious clinical problem which is accompanied by significant financial and emotional costs.

The healing process is a complex and well orchestrated physiological process that involves migration, proliferation and differentiation of a variety of cell types as well as synthesis of matrix components. Normally, the healing process comprises of three phases.

i) Haemostasis and inflammation  
When platelets are present outside the...

...derived growth factor (PDGF) and epidermal growth factor (EGF).

The first cells to invade the wound area are neutrophils followed by monocytes which are activated by macrophages. The major role of neutrophils appears to be clearing the wound of or defending the wound against contaminating bacteria and to improve the healing of the wound by removing dead cells and platelets. The infiltration of neutrophils ceases within about the first 48 hours provided that

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no bacterial contamination is present in the wound. Excess neutrophils are phagocytosed by tissue macrophages recruited from the circulating pool of blood-borne monocytes. Macrophages are believed to be essential for efficient wound healing in that they also are responsible for phagocytosis of pathogenic organisms and a clearing up of tissue debris. Furthermore, they release numerous factors involved in subsequent events of the healing process. The macrophages attack fibroblasts which start the production of collagen.

ii) Granulation tissue formation and re-epithelization

Within 48 hours after wounding, fibroblasts begin to proliferate and migrate into the wound space from the connective tissue at the wound edge. The fibroblasts produce collagens and glycosaminoglycans and inter alia low oxygen tension at the wound stimulates proliferation of endothelial cells. The endothelial cells give rise to the formation of a new capillary network.

Collagenases and plasminogen activators are secreted from keratinocytes. If the wound is left undisturbed and well-nourished with oxygen and

nutrients, keratinocytes will migrate over the The wound area is further decreased by contraction.

### iii) Dermal remodelling

As soon as the re-epithelization is completed the remodelling of the tissue begins. This phase, which runs for several years, restores the strength to the wounded tissue.

All of the above-mentioned healing processes take considerable time. The rate of healing is influenced by the wound's freedom from infection, the general health of the individual, presence of foreign bodies, etc. Some pathologic conditions like infection, maceration, drying out, generally bad health and malnutrition can lead to formation of a chronic ulcer.

Until at least superficial healing has occurred, the individual remains at risk of continued or new infection. Therefore, the quicker the wound can heal, the sooner the risk is removed.

Thus, any procedure that can influence the rate of wound healing or favourably influence the healing of wounds is of great value.

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Numerous treatments are currently used to create an optimal environment for the wound healing process. However, to our knowledge none of these treatments have been designed to

gn directly stimulate the wound repair process. It has previously been suggested that growth factors like epidermal growth factor (EGF...

...0) and insulin like growth factors (IGF-1 and IGF-2) are conductors of the wound healing process.

The present invention is based on a novel approach to wound healing, namely an approach involving the use of a wound healing composition comprising as an active wound healing substance a combination of two substances, where the first substance in the combination inter alia has a function of immobilizing the combination in the wound area in order to obtain an enhanced and/or sustained or prolonged effect, and the...

...is able to bind and/or activate and/or stabilize growth factors involved in the healing process. As will be explained in detail below, a particularly interesting combination according to the present invention is a combination between chitosan and sucrose octasulfate. Although both substances are known as promoters in the wound healing process, the combination according to the present invention has an unexpected useful, superior wound healing effect compared to the wound healing effect obtained by use of the individual substances alone or in a physical blend. Furthermore, the use of a combination according to the invention with the purpose of healing wounds is very advantageous; thus, in the case of chitosan-sucrose octasulfate the chitosan aids in immobilizing sucrose octasulfate (i.e. a wound healing agent) site specifically at/on the location at/on which the wound healing agent is to exert its effect. Moreover, the combination of e.g. chitosan-sucrose octasulfate has a water solubility which is much lower than that of sucrose octasulfate by itself.

If sucrose octasulfate is applied onto a wound, the pronounced water solubility of sucrose octasulfate will result in a very fast transport of ...lasting effect of sucrose octasulfate and, accordingly, sucrose

octasulfate has to be applied onto the wound very frequent (e.g. 3-7 times daily) in order to achieve the desired effect.

When treating many kinds of wounds specific precautions have to be taken into considerations, such as, e.g., sterility considerations, contamination problems, correct application of bandages / dressings etc. which normally require that the treatment/application is performed by well-educated nurses or the like, i.e. wound treatment becomes a very expensive operation when the wound healing agent is to be applied several times daily. A desired reduction in the costs involved in wound healing treatment is therefore obtainable when the application frequency can

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be reduced. By using a combination of e.g. chitosan and sucrose octasulfate it is possible to take advantage of the low water solubility of...

...on/at the application site and at that site slowly release sucrose octasulfate as a wound healing agent. The solubility of the sucrose octasulfate released at the desired site (wound) has been found to be of the same order of magnitude as that of sucrose...

...In addition to the beneficial The present inventors have found that although sucrose octasulfate and chitosan may react in situ after application of the two individual substances in vivo on a wound and form a combination of chitosan and sucrose octasulfate (this reaction takes place when the individual substances are applied in the...

...uncontrollable manner, i.e. resulting in a combination having an uncontrollable and variable content of chitosan and sucrose octasulfate, respectively. Therefore, even if chitosan and sucrose sulfate to a minor degree react with each other and form the desired combination in situ in/on a wound after application of the individual substances, the reaction is so uncontrollable and unreproducible that the ...

...determination of whether a combination according to the invention has a beneficial effect on the healing process. Reference is made to the following relevant tests but other tests may also prove suitable.

i) a test assessing epidermal regeneration (cf. A. Fourtanier et al., Br. J. of Dermatology

(1984) HI, Suppl. 27, 174-177,

ii) a test involving a diabetic mouse wound healing model (cf. B. Matuszewska et al., Pharm.

Res. (1994), Vol. 11, No. 4, 65-71),

iii) a test model for wound healing (cf. H.P. Dinger & H. Redl, Wiener klinische

Wochenschrift (1987), Vol. 99, No. 14, 497-501),

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iv) a test for the regeneration of full-thickness wounds (cf. M.J.A. van Luyn et al., J. Biomed.

Mat. Res. (1995), Nol. 29...

...3, 191-198),

vi) a test involving formation of e.g. a partial thickness excisional wound or a second degree burn wound (cf. P.M. Mertz et al.,

Cosmetics & Toiletties (1992), Vol. 107, 43-44), vii) a wound healing

- model in a scald burn injury pig model (cf. J.A. Bauer et al., Lipid Mediators Immunol. (1987), Vol. 139, 519...
- ...an organotypic in vitro model (cf. J.A. Garlick and L.B. Taichman, J. Invest. Dermatol . (1994), Vol. 103, 554-559), and
- ix) an in vitro model involving skin fibroblasts (cf. L.W. Adams & G.C. Priestley, Arch. Dermatol . Res. (1988), Vol. 280, 114-118).
- x) a test identifying wound healing associated indicators such as, e.g., indicators of pH, partial pressure O<sub>2</sub>, temperature, radical mechanisms...
- ...biotechnological assays, e.g.
- indicating a formation of collagen,
- xi) an in vitro model for wound healing wherein pieces of human skin is placed in a cell growth medium containing fetal calf serum (FCS); after fixation and...
- ...a light microscope,
- xii) in vitro tests designed for evaluation of components which impart the healing process (e.g. neutrophils, macrophages, fibroblasts, growth factors, collagen, collagenase, cell proliferation, and epidermal cell migration, i.e. epiboly) (e.g. cf. S.M. Vijayasingham et al., Br. J. Dermatol . (1991), Vol. 125, 136-139, and/or S. Regauer & C.C. Compton, J. Invest. Dermatol . (1990), Vol. 95, 341-346),
- xiii) a test involving basic fibroblast growth factor stimulation of epidermal wound healing in e.g. pigs (cf. P.A. Hebda et al., J. Invest. Dermatol . (1990), Vol. 95, 626-631), xiv) an in vitro test involving growing of a cell...
- ...the influence of the extracellular matrix on fibroblast responsiveness (cf. P.G. Genever, Br. J. Dermatol . (1995), Vol. 133, 231-235), and
- SUBSTITUTE SHEET (RULE 26)
- xv) a test involving histological...454 044 (both in the name of Hoechst Aktiengesellschaft) concerning polyelectrolytic complexes of e.g.

**chitosan** and dextran sulfate or xylan polysulfate are clearly without the scope of the present invention as the...invention.

Specific examples of interesting first compounds are compounds selected from the group consisting of **chitosan**, **chitosans** obtained by deacetylation of **chitin** to various degrees of deacetylation, **chitosan** derivatives, glycosaminoglycans including chondroitin, chondroitin sulfate, hyaluronic acid, **dermatan** sulfate and keratan sulfate; aminated dextrans including DEAE-dextran; aminated starch, aminated glycogen, aminated cellulose, aminated pectin, heparin, and salts, complexes, derivatives and mixtures thereof.

In particular **chitosan** and **chitosan** derivatives are promising candidates as a first compound.

Water-soluble **chitosan** has been described as an agent in the treatment

of wounds ; the chitosan is said to prevent the formation of fibrin strands (US Patent No. 4,532,134...of fibroblasts and the synthesis of collagen thereby allowing the promotion of normal tissue regeneration.

Chitosan has also been applied in the development of delivery systems as a means for obtaining controlled release of drugs (see e.g. WO 96/05810). Furthermore, chitosans have been found to have mucoadhesive properties (see e.g. EP 514 008, C-M. Lehr et al., "In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers, from C-M. Lehr's Ph.D.

thesis, 1991, Leiden University, the Netherlands) and the use of chitosan as an enhancer has been suggested.

Chitosans are considered as biocompatible macromolecules due to assumed low toxicity and biodegradability. They are degraded by lysozymes and related enzymes, such as N-acetyl-Dglucosaminidases. The lysozymic degradation of chitosan is believed to increase with the degree  
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of N-acetylation (see...

...rate of the second compound in a combination according to the invention (see below). Accordingly, chitosan for therapeutic use must be regarded as a safe substance.

Chitosan is a linear 1,4-bound polysaccharide built up from P-glucosamine entities. The chitosan is manufactured by N-deacetylation of chitin which is a naturally occurring polymer forming the shell of inter alia insects and crayfish. Commercial chitin is recovered from crab and shrimp shell which are waste products from the fishing industry. It is possible to manufacture chitosans of varying degrees of N-acetylation by controlling the reaction conditions (e.g. controlling the alkaline treatment of chitin). Furthermore, chitosan may be manufactured with different molecular weights (Antonsen et al., Carbohydrate Polymers, 22, 1993, 193-201). Different molecular weights of chitosan can be obtained by controlling the degradation of a high molecular weight chitosan in e.g. 1 N hydrochloric acid or by subjecting the chitosan to a controlled enzymatic degradation. When chitin is treated with alkali such as sodium hydroxide, Ndeacetylation takes place and the acetamido groups are converted into amino groups to form chitosan. Thus, in qualities of chitosan having a number of acetamido groups left, the aminosugar in the first compound of a...

...is believed that the degree of acetylation as well as the molecular weight of a chitosan have some impact on the properties of the combination formed. Thus, it is believed that...

...vivo release of the second compound from a combination (where the first compound is a chitosan) is subjected to at least one mechanism involving the degradation of the chitosan by an enzymatic process e.g. involving enzymes such as, e.g., lysozyme and proteases (present in wounds /ulcers), hyaluronidases, chitonases, metalloproteinases, collagenases, elastases and/or a combination thereof. As mentioned above, the lysozymic degradation of chitosan increases with the degree of N-acetylation and, accordingly, the release rate of the second...

...these release mechanisms seem to support the indication i) that the molecular weight of the chitosan comprised in the combination has an impact on the release rate (i.e. mainly for the release mechanism involving enzymatic degradation), and ii) that the degree of deacetylation of the chitosan comprised in the combination may have an

impact on the release rate (i.e. probably...

...as the degree of deacetylation also are important determinants for D the biodegradability of a **chitosan**, ii) the toxicity, iii) the degree of mucoadhesiveness, and iv) the enhancer effect.

Apart from...

...dissolved second compound such as, e.g., sucrose octasulfate, first compound such as, e.g., **chitosan** and/or the combination between the first and the second compound such as, e.g., **chitosan**-sucrose octasulfate respectively, may also be effective with respect to wound healing. Another possibility is that sucrose octasulfate (representative of a second compound) is capable of exerting its effect when at least some of the **chitosan** (representative of a first compound) is degraded to smaller fragments; an ion-exchange process may...

...sucrose octasulfate.

Thus, in particular preferred embodiments of the invention, the first compound is a **chitosan**, especially a **chitosan** which has a molecular weight in a range of about 3,000 to about 1,500,000 daltons. With respect to the degree of deacetylation, the **chitosan** notably has a degree of deacetylation of at the most 100% such as at the most 99%, 95%, 90%, 85%, or 80%, or expressed in another way the **chitosan** has a degree of deacetylation in a range of about 10-90% such as about...

...50-75%, about 60-85%, about 75-85%, or about 80-90%.

The concentration of **chitosan** in the combination is in a range of ... evidenced as described above), which is capable of releasing the second compound e.g. in wounded tissue, and which is biocompatible and biodegradable. A proviso for such other kinds of suitable...

...of the total combination.

In a particularly important embodiment, the combination is formed between a **chitosan** as the first compound and a sucrose octasulfate as the second compound.

The **chitosan** may be **chitosan** polymer having a molecular weight in a range of from 10 kdalton to 1500 kdalton and a degree of deacetylation in a range of at the most 100%. **Chitosan** is presently available in qualities having a mean molecular weight in a range of from...

...a degree of deacetylation in a range of from about 75% to about 85%, but **chitosans** of other mean molecular weights and having other degrees of deacetylation are obtainable by employment of methods well known to a person skilled in the art (cf. above). Examples of **chitosans** are **chitosan**, Wella "low viscosity", ...C., Wella "high viscosity", C., Dr. Knapzyk, Daichitosan H, Daichitosan VH, SeaCure 240, SeaCure 210, **Chitosan** (Sigma), Polycarbophil/daichitosan VH blend, Protasan CL 210, Protasan G210, and Protasan G110.

Furthermore, **chitosans** having a mean molecular weight of about 70,000-500,000 such as about 250...

...may be interesting candidates as first compounds in a combination according to the invention. The **chitosan** may be in the form of a **chitosan** base or in the form of a salt such as, e.g., a glutamate, a lactate, or a hydrochloride salt. Mixtures of **chitosan** base and one or

more **chitosan** salts are within the scope of the present invention as well as mixtures of **chitosans** having different mean molecular weights and/or degrees of deacetylation.

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An...

...a combination according to the invention is a combination wherein the first compound is a **chitosan** having a molecular weight in a range from about 5,000 to about 100,000...

...prevention of any relevant conditions, especially in conditions involving tissue repair such as in the **healing** of **wounds**. Furthermore, when the combination is a combination of a **chitosan** and a sucrose octasulfate, the combination may be used in the treatment or prevention of...

...for any condition which respond positively to a treatment with sucrose octasulfate.

A combination of **chitosan** as a first compound and a sucrose octasulfate as a second compound is believed to have properties which are highly valuable in connection with **wound** treatment.

Thus, **chitosan** is a biocompatible and relatively slowly biodegradable compound and sucrose octasulfate is also biodegradable. A combination of these two compounds is therefore believed also to be biodegradable. As mentioned above, **chitosan** is degraded in vivo by enzymes, e.g.

lysozyme, proteases, and/or other enzymes present...

...number of body fluids and is released by leukocytes and other cells normally present in **wounds** and other tissues where tissue repair is ongoing. A working theory for a combination of **chitosan** and sucrose octasulfate is that when the combination is applied to a **wound** or a tissue which is to be repaired, then the lysozyme and/or protease present ...most important use of a combination according to the invention is the use as a **wound healing** agent, i.e. an agent which accelerate, stimulate or promote **healing** of **dermal** or **mucosal wounds**. Yet another important use, is the use as a tissue repair agent. The term "**wound**" used in the present context denotes any **wound** (see below for a classification of **wounds**) and at any particular stage in the **healing** process including the stage before any **healing** has initiated.

A composition according to the invention will typically stabilise and/or stimulate fibroblast growth factors (FGF), the formation of collagen or the **healing** of **wounds** in vitro when subjected to relevant test like the tests described herein.

In general, the term "**wound**" denotes a bodily **injury** caused by physical means, with disruption of the normal continuity of structures. Examples of **wounds** are, e.g., contused **wounds**, incised **wounds** In general **wounds** may be classified as follows.

D Mechanical **injuries** (e.g. **abrasion**, **lacerations**, penetrating **wounds**, bites, and surgical ii) Burns and chemical injuries [e.g. superficial burns (first degree), deep **dermal burns** (second degree), and full thickness (third degree)],  
iii) Chronic ulcerative **wounds**  
a) decubitus ulcer also called bed or pressure sores  
b) leg ulcers (venous, ischaemic or **traumatic**)



O ulcers associated with certain systemic infections  
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d) ulcers resulting from radiotherapy  
e) ulcers resulting from malignant diseases.

In general **wounds** may also be classified by appearance as follows.  
i) black and necrotic **wound** covered with a hard, dry black necrotic layer (e.g. small and superficial **wounds** or extensive and deep **wounds** )  
ii) yellow and sloughy **wounds** covered with (or filled) with a soft yellow slough (e.g. small and dry **wound** , small and moist **wounds** , and large deep cavities containing semi-liquid necrotic material)  
iii) clean **wounds** with significant tissue loss (granulating **wounds** such as, e.g., clean surgical **wounds** with significant tissue loss, chronic **wounds** with low to moderate exudate, chronic open **wounds** with moderate to high exudate, and chronic flask-shaped **wounds** ) iv) clean and superficial **wounds** (epithelialising **wounds** such as, e.g., clean, low exudate v) clinically infected **wounds** (such as, e.g., extensive or heavily exuding **wounds** , small cavities or craters, and shallow open **wounds** )  
vi) malodorous **wounds** (e.g. infected pressure sores, fungating carcinomas, etc.) In connection with treatment of **wounds** /ulcers debridement and **wound** cleansing are of particular importance. It is believed that the cleaning and/or debridement of **wounds** /ulcers are a prerequisite for the **healing** process and, furthermore, when **wound healing** agents are applied such agents have to exert their effect on fresh and vital tissue...debridement is normally performed in operating room and sterile instruments are used.

Furthermore, clean, dry **dressing** should be applied.

Mechanical debridement includes the use of wet-to-dry **dressing** at prescribed intervals, hydrotherapy, **wound** irrigation and dextranomers.

Enzymatic debridement is often used in long-term care facilities and in ...

...debriding agents to devitalized tissue on the Autolytic debridement is accomplished by placing a synthetic **dressing** over the ulcer and allowing the eschar to self-digest through the action of enzymes normally present in the **wound** fluid. Autolytic debridement is contraindicated in infected ulcers.

When the ulcer/ **wound** has been subjected to debridement, a combination according to the invention or a composition containing the combination can be applied either directly on or into the **wound** or ulcer or it can be applied in the form of a dry or moist, clean **dressing** into which the combination has been incorporated.

The combination according to the invention may of course also be applied in connection with cleansing of the ulcer/ **wound** . Ulcer **wounds** should be cleansed initially and at every **dressing** change. The process of cleansing a **wound** involves selecting a **wound** -cleansing solution and a mechanical means of delivering that solution to the **wound** .

A combination according to the present invention may be used for any **wound** /ulcer independent of its ethiology, nature or **healing** stage. It may be used for curative purposes as well as for preventive purposes. Furthermore...a free amount of first and/or second compound. Especially a

free amount of a wound healing agent such as, e.g. sucrose octasulfate and/or chitosan may in certain cases be desired especially in those cases where a rapid onset of...cause of the ulcer. Such a composition would have two objectives, namely i) to impart wound healing and ii) to treat the underlying disease to the formation of ulcers. In this case, the wound is used as the application site for delivery of a further active drug substance to...

...system. It is contemplated that the access to the circulatory system is much easier via wounds /ulcers than via intact skin .

Vaccines are also interesting candidates for a delivery to the circulatory system via a Other...

...an emulsion, tablets, capsules, pills, powders, granulates, gels including hydrogels, lotions, pastes, ointments, creams, drenches, dressings , hydrogel dressings , hydrocolloid dressings , films, foams, sheets, bandages , plasters, delivery devices, suppositories, enemas, implants, aerosols, microcapsules, microspheres, nanoparticles, liposomes, and in other suitable form.

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Compositions for application to the skin or to the mucosa are considered most important in connection with the present invention. Thus ...

...be administered may be adapted for administration by any suitable route, for example by topical ( dermal ), oral, buccal, nasal, aural, rectal, vaginal, pulmonal administration, or by administration to a body cavity ...

...with surgery, e.g. in connection with incision within the body in order to promote healing of internal wounds and tissue damage such as bone fractures.  
The compositions may be formulated according to conventional...

...the application of a composition comprising a combination according to the invention is intended for skin or mucosa. Other applications may of course also be relevant such as, e.g., application...great importance. Relevant examples are application to periodontal (dental) pockets, to gingiva or to gingival wounds or ulcers, or in connection with dental surgery.

The pharmaceutical composition comprising a combination according...

...ointments, liquids, powders, tablets, etc. as well as more sophisticated formulations such as sprays, plasters, bandages , dressings , devices, etc.

Pharmaceutically acceptable excipients - dosage forms

Apart from the combination, the pharmaceutical compositions according...

...is generally dependent on the dosage form suitable for use for a particular kind of wound /ulcer. In the following is given a detailed list of suitable pharmaceutically acceptable excipients for...  
...basis of an experimental evaluation of the final composition.

#### Topical compositions

For application to the skin , the formulations according to the invention may contain conventionally non-toxic pharmaceutically

acceptable carriers and...

...lotions, liniments, gels, hydrogels, solutions, suspensions, sticks, sprays, pastes, plasters, films, powders, soaps, shampoos, jellies, dressings such as absorbent wound dressings, pads, bandages, foams, plasters, and transdermal drug delivery systems.

The pharmaceutically acceptable excipients may include emulsifying agents, antioxidants, buffering agents, preservatives, humectants, penetration enhancers, chelating agents, gelforming agents, ointment bases, perfumes, and skin protective agents.

Examples of emulsifying agents are naturally occurring gums, e.g. gum acacia or...

...alcohols; sorbitan esters; monoglycerides; and fatty alcohols.

Examples of antioxidants are butylated hydroxy anisole (BHA), ascorbic acid and derivatives thereof, tocopherol and derivatives thereof, butylated hydroxy anisole, and cysteine.

Suitable examples of...Examples of gel bases or components which are able to take up exudate from a wound /ulcer are.

liquid paraffin, polyethylene, fatty oils, colloidal silica or aluminium, zinc soaps, glycerol, propylene...

...magnesiumaluminium silicates, Carbopol, hydrophilic polymers such as, e.g. starch or cellulose derivatives, liquid absorbing wound bandages, water-swellaable hydrocolloid, and alginates.

Examples of powder components are: alginate, collagen, lactose, powder which is able to form a gel when applied to a wound /ulcer (absorbs liquid/ wound exudate). Normally, powders intended for application on large open wounds must be sterile and the particles present must be micronized.

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Alginic...

...present invention. As explained above, alginates can form a gel and, furthermore, they can absorb wound exudates and thus contributing to controlling the moisture content of a wound. Alginic acid and alginates are available in various qualities having a mean molecular weight in...

...compositions include tackifier resin, viscous elastomeric binders, elastic film, elastic adhesive material, elastomers and plasticizers.

Dressings and/or bandages are also important delivery systems for a combination according to the invention. Dressings may be in the form of absorbent wound dressings for application to exuding wounds. Such dressings are frequently made of cotton or viscose fibres which are enclosed in a sleeve of gauze or a suitable non-woven fabric. Other relevant materials are cellulose fibres, cellulose wood pulp (fine powdery material). Dressings may also be in the form of hydrogel dressings such as, e.g., i) dressings having a fixed three-dimensional macrostructure, and ii) dressings involving amorphous hydrogels. In the latter case, the dressings progressively decrease in viscosity when the material absorbs fluid, and the dressing may then flow on top of the wound and take on the shape of the wound. Examples of other kinds of dressings are i) hydrocolloid dressings (gel-forming agents combined with other material such as, e.g. elastomers and adhesives) including...

...or paste and hydrocolloid sheet, ii) alginate sheet (rope or ribbon, alginate with integral absorbent pad), iii) foams (foam dressings, silastic foam, polyurethane foam), iv) various polysaccharide materials, v) occlusive dressings, vi) semipermeable dressings, vii) paraffin gauze dressings, viii) Tulle dressings, ix) polysaccharide pastes, granules and beads (may be manufactured from dextran derivatives), and x) odour-absorbing dressings. Suitable bandages may be i) non-extensible bandages, ii) extensible bandages, iii) adhesive/cohesive bandages, iv) tubular bandages, v) medicated paste bandages, and vi) orthopaedic casting materials.

Semipermeable films and thin foam sheets have little or no intrinsic absorbent capacity. They are permeable to moisture vapour when placed on a wound and, accordingly, the aqueous component of a wound exudate is lost through the backing of the dressing in the form of a vapour. The cellular material remains trapped at the surface of the wound.

Alginate and hydrocolloid dressings take up wound exudate when placed on a wound. When doing so they produce an aqueous gel on the surface of the wound and this gel is believed to be beneficial for the healing of the wound due to the retaining of moisture in the wound.

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The compositions mentioned above for topical administration are most suitable for application directly to wounds or they may be suitable for application to or for introduction into relevant orifice(s...

...route of administration.

Fluid/liquid compositions for oral use or for application to mucosa or skin. Compositions like a suspension, an emulsion or a dispersion provide the combination in admixture with...

...the gastrointestinal, buccal, nasal, rectal, or vaginal mucosa, or for administration to intact or damaged skin, or wounds /ulcers.

Suitable dispersing or wetting agents are, for example, naturally occurring phosphatides, e.g., lecithin...of solvent chosen for the reactants, any addition of accelerators, the ratio of SOS and chitosan, the pH prevailing in the reaction mixture, reaction time, rotation speed, e.g. from 0...

...cooling of the reaction mixture, employment of ultrasonic treatment (cf. Example 5), the starting materials (chitosan, chitosan glutamate, chitosan chloride, chitosan lactate, sucrose octasulfate as hydrate or other solvates or as a sodium, potassium or another...bioadhesive due to the properties of the first compound (which e.g. may be a chitosan as described above). Administration of a bioadhesive combination may enable a localized effect as the...Ramipril

Lisinopril

Antihyperlipoproteinemic agents.

Acifran

Acipimox

Ciprofibrate

Clinofibrate

Clofibric acid

Pravastatin sodium

Fluvastatin

Gernfibrozil

Meglutol

Nicotinic acid  
Oxiniacic acid  
Antiamebic agents.

Thiocarbarnizine  
Luteolytic agents.

Tiaprost  
Antiulcerative agents.

Arbaprostil  
Carbenoxolone  
Cetraxate  
Rebarnipide  
Rosaprostol...

...Cromolyn

Especially interesting combinations according to the invention are combinations wherein the first compound is **chitosan** and the second compound is any of the above-mentioned active drug substances or combinations...

...is not

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restricted to combinations which are suitable for use as **wound healing** agents but for any appropriate therapeutic/prophylactic use. In those cases in which the combination...the heat now in mW against the temperature (0Q.

Fig. 2 shows a thermograin of **chitosan**. The experimental details are as described under Fig. 1.

1.600 mg of **chitosan** was used.

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Fig. 3 shows a thermogram of a combination of **chitosan** and SOS (batch No. AAAS 1). The experimental details are as described under Fig. 1. 5.640 mg of **chitosan** -SOS was used.

Fig. 4 shows a thermogram of a physical blend of **chitosan** and sodium sucrose octasulfate. The experimental details are as described under Fig. 1. The physical blend used consisted of about 4 mg **chitosan** and about 21 mg sodium sucrose octasulfate.

Fig. 5 shows the results of a number of syntheses of **chitosan** -SOS in which the initial concentration of sodium sucrose octasulfate has been varied in order...

...The graph is a plot of the loading of sodium sucrose octasulfate (Na-SOS) to **chitosan** (solution of Protasan CI 210 2 mg/ml) versus the initial concentration of sodium sucrose...

...mixture.

#### MATERIAL AND METHODS

##### Materials

The following qualities of a poly-D-glucosamine, i.e. **chitosan**, have been used in the Examples described below.

**Chitosan** base available from Sigma, practical grade  
Seacure CL 310, Pronova Biopolymer a.s., Norway, (viscosity...

...about 80%)

Protasan G110, Pronova Biopolymer a.s., Norway, (viscosity 10mPas)  
The different grades of **chitosan** and **chitosan** salts are specified by the mean molecular weight, the degree ...acid, Brookfield LVT viscometer, 25'C, 30 rpm)). Pronova. Biopolymer a.s., Norway supplies two **chitosan** salts, namely the glutamate and the hydrochloride salt, both in two-different qualities. Protasan is...

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Seacure is a product of regular quality. The degree of deacetylation of **chitosan** and **chitosan** salts is normally about 84%

Sodium sucroseoctasulfate available from BM Research, Denmark, water content of...

...gels, creams@ oils, lotions, foams, etc. with or without a content of a combination of **chitosan** -SOS according to the invention) is determined using a RheoStress RS 100 Rheometer, HAAKE (Germany...read at different times, e.g. at t= 180 sec.

#### EXAMPLES

##### EXAMPLE 1

Preparation of **chitosan** solutions

**Chitosan** base is not soluble at pH above 7.0 and, therefore, the pH must be...

...avoid precipitation.

A 1% w/v solution is prepared by slurring e.g. 2 g **chitosan** (Sigma, practical grade) in 100 ml of distilled water followed by adding 100 ml of...

...solution of acetic acid. The resulting mixture, i.e. a 1% w/v solution of **chitosan** in 1% w/v acetic acid, is stirred vigorously for 60 minutes or until dissolution...

...accelerate the dissolution process, but prolonged heating may result in a decrease in viscosity. Alternatively, **chitosan** can be dissolved directly by adding **chitosan** to a 1% w/v acetic acid solution. 2% w/v solutions of **chitosan** (Sigma, practical grade) in 1% w/v can also be prepared.

Alternatively, **chitosan** may be dissolved under vigorous stirring for 24-48 hours.

1% w/v and 2% w/v solutions of **chitosan** glutamate and **chitosan** hydrochloride can easily be made in water.

##### EXAMPLE 2

Formation of **chitosan** -SOS beads

A solution of 1% w/v (10 mg/ml) **chitosan** (Sigma) in 1% w/v acetic acid is pumped dropwise through a tip from a...

...salt (SOS-Na8) in distilled water.

Beads (drops or pearls) appear in the solution as **chitosan** gets into contact with SOS-Na8 presumably forming a combination or complex on the surface of the **chitosan** beads. The beads are approximately 2 mm in diameter and the surface becomes opaque whitish...

...a very hard material which is not easily pulverized.

### EXAMPLE3

Preparation of a combination of **chitosan** and SOS-Na8

An aqueous solution containing 12.5 mg sucrose octasulfate sodium salt (SOS-Na8) is added to a solution of 1% w/v **chitosan** in 1% w/v acetic acid under vigorous stirring. A flocculate or flakelike precipitate is... the invention are described.

In the following details are given on the preparation of various **chitosan** -sodium sucroseoctasulfate combinations.

Solutions used.

I Solutions of **chitosan** (deacetylation grade 75-85%, concentration: 1% w/v (10 mg/ml) in 1% w/v acetic acid; the **chitosan** employed may be either **chitosan** base, **chitosan** hydrochloride or **chitosan** glutarnate. In the following **chitosan** has been employed as the base unless otherwise specified.

II Aqueous solutions of sodium sucrose...

...period of 40 min. The reaction time is 40 min. Small transparent spheres containing the **chitosan** solution are formed. The **chitosan** solution reacts slowly with sucrose octasulfate on the surface  
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of the...

...dried 4 hrs in a fume cupboard or for 2 hours at 60°C. The **chitosan** solution is dried in an oven (40-60°C) until nearly dryness and a soft film is obtained. Alternatively, the **chitosan** solution is dried to dryness either at room temperature or in an oven (conditions as...

...Mm is obtained, the film can easily be softened with water. To the thus obtained **chitosan** film, 20 ml of II (12.5 mg/ml) is added and left to evaporate...

...The use of the same method given above for the preparation of a combination of **chitosan** and SOS resulted in products having the same visual appearance, but the appearance of the...

...properties that are different from those of the pure materials and a physical blend of **chitosan** and SOS-Na8- In the following table is given a review of the method used for the preparation of various batches of **chitosan** -SOS ...Na8 dissolved in 100 ml of distilled water is added to 50 ml of a **chitosan** solution (cf. Example 1) by means of a syringe and a canula and with vigorously...

...is filtered off and dried at ambient temperature.

AAAS5-2: As AAAS5-1 but the **chitosan** solution is added to the SOS-Na8-solution.

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AAAS7-2: 10 ml of a **chitosan** solution (cf. Example 1) is dropwise added to 100 mg SOS-Na8 in 40 ml distilled water.

AAAS7-6: 10 ml of a **chitosan** solution (cf. Example 1) is dropwise added to 0.5 g SOS-Na8 in 40...

...water is slowly added through a tip for a pipette to 10 ml of a **chitosan** solution (cf. Example 1), yield 0.1280 g.

AAAS11-6: 0.500 g SOS-Na8...

...water is slowly added through a tip for a pipette to 10 ml of a **chitosan** solution (cf. Example 1), yield 0.1749 g.

AAAS12-4: 10 ml of a **chitosan** solution (cf. Example 1) is dropwise added to 0.150 g SOS-Na8 in 40 ml distilled water, yield 0.1825 g.

AAAS12-6: 10 ml of a **chitosan** solution (cf. Example 1) is dropwise added to 0.500 g SOS-Na8 in 40 ml distilled water, yield 0.1638 g.

AAAS13b-4: a **chitosan** Mm is formed by completely drying of a 1% **chitosan** solution. Then 0.4 g SOS-Na8 dissolved in 20 ml water is added.

AAAS13c...

...by Method III given above in the reverse order.

AAAS15-1 and AAAS15-3: A **chitosan** solution (cf. Example 1) is poured into a petri dish and a **chitosan** film is obtained after evaporation of the solvent. Then a solution of SOS-Na8 is...

...e. equivalent to Method III given above)

Various other preparations have been performed, e.g. **chitosan** has been employed in form of its glutamate or its hydrochloride. However, the initial results...63\*, 65@ 6% 71 (Protasan CL 210, batch 6061703)

AAAS 66 (0.5% w/v **chitosan**, Seacure CL 313, batch 7010301)

AAAS 79 contains the batches AAAS 64, 67, 70, 72...

...6 +/- 0.16 (including free SOS present) \* = prepared from 100 ml 0.1% w/v **chitosan** solution and 400 ml 1.25% w/v SOS solution Method IV 500 ml of **chitosan** solution (10 mg/ml) is added slowly and dropwise by a pump (Watson-Marlow), rate...

...ml of SOS solution (12.5 mg/ml) at room temperature. The 500 ml of **chitosan** solution is added over a time period of about 3 hours. Small transparent spheres containing the **chitosan** solution are formed. The obtained mixture is allowed to react for 4 hours from start of the experiment. The **chitosan** solution reacts with SOS on the surface of the drops and small spheres are formed and filtered off using a paper filter. Washing procedure.

I The **chitosan** -SOS formed is subjected to a washing procedure in order to remove any unbound or loose bound water-soluble SOS. The washing procedure involves suspending of the **chitosan** -SOS in about 200 ml of distilled water while stirring.

The liquid is filtered off...

...60'C for 2 hours. Dried flakes are obtained.

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II The **chitosan** -SOS formed is subjected to a washing procedure in order to remove any unbound or loose bound water-soluble SOS. The washing procedure involves suspending of the **chitosan** -SOS in about 200 ml of distilled water for 15 min while stirring. The liquid...

...an oven at 60'C for 2 hours. Dried flakes are obtained.

Milling of the **chitosan** -SOS.



The products obtained are clear and very hard flakes having a pale yellowish colour...electrolyte solution.

Method IV and Washing procedure II have been employed in the preparation of **chitosan** -SOS combinations of varying degrees of loading with SOS. Many of the batches mentioned above...

...unbound and loose bound SOS). The combinations are prepared starting from the following ratios of **chitosan** :SOS (w/w) and with 100 g **chitosan** (Seacure Cl 313) as starting material.

1. Batch BHQ01 1:1 (the resulting product was...

...very small yield)

4. Batch BHQ03 2:1 (pale white drops)  
The solutions used were.

**Chitosan** solution: A 1% w/v (10 mg/ml) **chitosan** solution is prepared by slurring 5.0 g **chitosan** in 250 ml of distilled water followed by adding 250 ml of a 2% w...

...solution of acetic acid. The resulting mixture, i.e. a 1% w/v solution of **chitosan** in 1% w/v acetic acid, is stirred vigorously for 60 min or until dissolution has taken place. Alternatively, the **chitosan** can be dissolved directly in 1% acetic acid solution.

SOS solution: 1, 2.5, 5...

...is determined.

Elemental analysis is also performed and the results are the following.

#### Results

Batch **Chitosan** : Nitrogen Sulphur mol mol g SOS per 100 g  
Na8-SOS M M sulphur SOS...

...33J

BHQ02 1:5' 4@3 %3 O@291 0,036 3521

a 2 mg **chitosan** /ml to 1 mg Na8-SOS/ml

b 2 mg **chitosan** /ml to 2 mg Na8-SOS/ml

' 2 mg **chitosan** /ml to 10 mg Na8-SOS/ml

The results show that the load increases with increasing concentrations of SOS solution employed. Furthermore, it seems as if the maximal loading of **chitosan** with SOS is almost reached.

The products obtained were subjected to testing for free, unbound... contains about 12% sulfur and 3% nitrogen corresponding to about 45% SOS and about 55% **chitosan** (including loose bound and unbound SOS)

the use of different qualities of **chitosan** with the same degree of deacetylation corresponding to about 84% (Protasan CL 210 and Seacure...

...of solvent chosen for the reactants, any addition of accelerators, the ratio of SOS and **chitosan**, the pH prevailing in the reaction mixture, reaction time, rotation speed, e.g. from 0...

...cooling of the reaction mixture, employment of ultrasonic treatment (cf.

Example 5), the starting materials (**chitosan**, **chitosan** glutarnate, **chitosan** chloride, **chitosan** lactate, sucroseoctasulfate as hydrate or

other solvates or as a sodium, potassium or another salt) and the concentration thereof (the concentration of **chitosan** may be varied from about 0.1% to about 20% w/v and the concentration...

...Investigations are still ongoing with regard to testing relevant process parameters.

#### EXAMPLE 5

Preparation of a **chitosan** -sodium sucrose octasulfate film

(see also method III described in Example 4)

10 ml of a 1% w/w solution of **chitosan** (Sigma) in 1% w/w acetic acid is poured into a petri dish (9 cm...

...alternatively, the solvent is evaporated in an oven at 40-60°C resulting in a **chitosan** Mem.

Then 20 ml of an aqueous solution of sodium sucrose octasulfate (SOS-Na) is poured on the dried **chitosan** and left at ambient temperature. After 24 hrs a milky precipitate is formed and a soft film is obtained.

A **chitosan** -sodium sucrose octasulfate film can also be obtained starting from pouring a sodium sucrose octasulfate solution into a petri dish and then adding a **chitosan** solution thereto.

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#### EXAMPLE 6

Characterization of a **chitosan** -sodium sucrose octasulfate combination (batch AAAS

5-2 and batch AAAS 82)

A. Differential Scanning Calorimetry

The following materials were subjected to Differential Scanning Calorimetry.

Batch AAAS 2 ( **chitosan** -SOS combination)

Sodium sucrose octasulfate from BM Research

**Chitosan** (C-3646) from SIGMA

A physical blend of 25 mg of sodium sucrose octasulfate and 5 mg of **chitosan** (5:1) (The ratio between SOS-Na8 and **chitosan** has proved not to have any significant influence on the result

The thermograms obtained are enclosed (see Fig. 1-4) and they show that

i) **chitosan** decomposes at about 230°C;

ii) sodium sucrose octasulfate has a sharp endotherm at about 100...

...hydrate.

iii) sodium sucrose octasulfate decomposes at about 150°C;

iv) the physical blend of **chitosan** and sodium sucrose octasulfate shows a sharp endotherm at about 100°C, a decomposition of sucrose octasulfate at about 150°C and a decomposition of

**chitosan** of about 230°C;

v) the AAAS 2, i.e. the **chitosan** -sodium sucrose octasulfate combination, has none of the above-mentioned characteristics, i.e. the thermogram...

...any endotherm at 100°C nor shows it any decomposition of sodium sucrose octasulfate and **chitosan** at about 150°C and about 230°C, respectively.

In conclusion, the AAAS 2, i.e. the **chitosan** -sodium sucrose octasulfate combination, shows thermal properties which are different from the individual materials as well as from a physical blend of the individual

materials, i.e. the **chitosan** -sodium sucroseoctasulfate combination is not a mere physical blend of the materials.

#### B. Solubility SUBSTITUTE...

...to about 50'C on a ultrasonic bath for 30 min.

The solubility of the **chitosan** -sodium sucroseoctasulfate combination (pulverized in a mortar) was investigated in the following media.

1. hydrochloric...described in USP 23 (1995) page 1443

None of the above-mentioned media dissolved the **chitosan** -sodium sucrose octasulfate combination under the conditions given above (heating at 50'C on a...

...mg/ml).

SOS-Na8 is also soluble in 1% w/v acetic acid.

Solubility of **chitosan** (as base) in the above mentioned media.

As mentioned above, **chitosan** is not soluble at pH above 7.0; therefore, to avoid precipitation, the pH must...

...maintained at pH 6.0 or below.

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Generally the solubility of **chitosan** in inorganic acids is as follows.

HCl/HNO3: **Chitosan** is soluble in a 0.1.1 % solution of the acid but insoluble in a...

...concentration.

H3PO4: Only slightly soluble in a 0.5% solution of the acid.

Solubility of **chitosan** in the above mentioned media and under the conditions given: not soluble in media 1...

...M HCl with sodium chloride), 3, 4, 5 and 6.

In media I and 2 **chitosan** is only sparingly soluble after 30 min on the ultrasonic bath.

However, additional experiments have indicated that **chitosan** is soluble in hydrochloric acid but the solubility rate is very slow. Furthermore, **chitosan** is soluble in weak organic acid such as in 1% w/v acetic acid.

A preferred method to make a 1 % **chitosan** solution is to slurry the **chitosan** in water and then add the solution of the desired organic acid (normally acetic acid...

...mixture should be stirred vigorously for 60 minutes or until complete solubility is realized. Alternatively, **chitosan** can be dissolved directly by adding **chitosan** to a prepared 1 % solution of the organic acid.

The solubility may also be determined...g. 24 hours or longer, if necessary.

Solubility of AAAS 82

The aqueous solubility of **chitosan** -SOS (AAAS 82) (premilled to a mean particle size of about 50-60  $\mu$ m) was...

...saturation equilibrium was established. A concentration range of SUBSTITUTE SHEET (RULE 26)  
PCT/DK97/00525 **chitosan** -SOS in the solvents was examined. The solubility was assessed by visually inspection of undissolved particles in the glass containers.

It was found that the aqueous solubility of **chitosan** -SOS (premilled AAAS 79) in both deionized water and in 0.9% w/v sodium...

...respectively, is less than 0.001 mg/ml (1  $\mu$ g/ml).

Furthermore, the solubility of **chitosan** -SOS in 1 M aqueous ammoniumchloride (pKA 9.25) pH 5.0 has been found to be less than 0.01 mg/ml.

In conclusion, SOS-Na8 and **chitosan** are dissolved in 1% w/v acetic acid and in weak acid solutions whereas a combination of **chitosan** -SOS-Na8 is insoluble in 1% w/v acetic acid.

Furthermore, variation in the composition of **chitosan** and SOS (e.g. the load of SOS on **chitosan** ) may give rise to a variation with respect to solubility properties and other physicochemical properties...

...0.1 mg/ml using the above-discussed method.

C. Release of sodium sucroseoctasulfate from a **chitosan** -sodium sucrose octasulfate

combination by means of lysozyme

Lysozyme is an enzyme which is present in wounds of mammals and, furthermore, Lysozyme L 6876 from Sigma is able to hydrolyze **chitosan** to glucosamine residues. The aim of the study was to investigate whether the influence of lysozyme on a **chitosan** -sodium sucrose octasulfate combination releases sodium sucrose octasulfate from the combination.

The following experiments were...

...to have substantial documentation).

1. to 40.0 mg of AAAS 2 (i.e. a **chitosan** -sodium sucroseoctasulfate combination) was added 1.0 ml of 1.0% w/v lysozyme dissolved...

...then diluted to 50.0 ml with distilled water

2. to 10.0 mg of **chitosan** was added 1.0 ml of 1.0% w/v ...experiment 1 and 3 showed clear solutions, i.e. the materials had reacted/dissolved. The **chitosan** in experiment 2 had not completely degraded. The result indicate that a reaction has taken place in experiment 1 whereas the degradation of **chitosan** itself was not completed within the test period (2 hours).

The amount of sodium sucrose...

...in exp. 3 (based on the initial concentration of SOS in the solutions). Hydrolysis of **chitosan** with lysozyme releases SOS but, apparently, lysozyme or the conditions prevailing also seems to have...

...and has its the maximum activity at about pH 5).

D. Elemental analysis of a **chitosan** -sodium sucroseoctasulfate

combination (batch AAAS 2  
and AAAS19)  
AAAS19 was made according to method I...

...the SOS-content in the combination.

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E. Determination of pH of **chitosan** and sucrose octasulfate containing solutions 10 ml of a solution of 1% w/v **chitosan** in 1% w/w acetic acid was added to 6 different aqueous solution (40 ml...mg/ml. After a reaction time of 40 min, the precipitated solid material (combination of **chitosan** and SOS-Na8 according to the invention) was filtered off and pH was measured in the filtrate.

3 different solutions of **chitosan** were employed and the three different types of **chitosan** described under "Materials" were employed. Thus, totally the pH of 18 filtrates was measured.

#### Results.

A solution of **chitosan** from SIGMA added to the 6 solutions of SOS all gave a pH about 4...

...gave a pH about 3 The difference in molecular structure between the three types of **chitosan** can explain the difference in pH (especially the deacetylation grade of the **chitosan** may be of importance here).

Finally, pH was measured in six aqueous solutions of SOS...

...detected by a photographic film wrapped around the circumference of the camera.

#### G. Other investigations

**Chitosan** -SOS combinations were precipitated in 6 different aqueous solutions of SOS (conc.range 1.25...be obtained by varying the preparation conditions such as, e.g., the concentration of the **chitosan** solution and the concentration of the SOS solution.

The results of this experiment do not...

...some kind of binding forces may be operating. Without being bound to any theory, the **chitosan** -SOS in the combination may be based on the following structures.

complex  
ionic binding  
gel...

...structure of the combination.

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##### EXAMPLE 7

In vivo investigation of the wound healing effect of a **chitosan** -sodium sucroseoctasulfate combination

A. A clinical study of donor site healing after autologous split skin transplantation The aim of the study is to document a potential benefit of using a combination of **chitosan** -SOS in the healing of skin wounds .

Twenty patients with preferably two split donor sites receive randomly

selected between the two donor sites, traditional wound dressing (control) or traditional wound dressing plus chitosanSOS combination (test). Wound dressings are changed every two days and time to complete healing of the donor site is recorded.

B. A clinical study of treatment of leg ulcers...

...ulcers are a very important clinical problem demanding large resources in both primary and secondary healthcare service and incapacitating a high number of the elderly people.

A randomised study of healing of leg ulcers in two parallel patient groups. Patients from a wound treatment clinic with ulcers that is expected to be able to heal, and not to be treated with skin transplant are selected for the study. Leg ulcers receive traditional treatment (control) or traditional treatment plus a chitosan -SOS combination or alternatively, leg ulcers receive placebo (control) or treatment with a combination according...

...ulcer closure rate" calculated after measuring ulcer area weekly.

Secondary end points are time to healing and overall number of completely healed ulcers in the two study groups.

#### EXAMPLE 8

Assessment of tissue reactions to different wound dressing in full thickness wound study in pigs

Before a study as the one described in the following is started assess the tissue reactions in full thickness wounds in pigs after treatment with the following four test samples.

TA-1: chitosan

TA-2: sodium sucrose octasulfate

TA-3: a combination of chitosan -sucrose octasulfate according to the invention

TA-4: a physical blend of chitosan and sodium sucrose octasulfate

TA-5: no treatment

As control the following can be used...

...HX pharm. in distilled water containing the test substance. Gels containing 5-40% w/w chitosan -SOS was prepared by slowly adding the polymer powder to the water phase heated to...

...stirred until a homogeneous clear colourless solution was obtained. 5-40% w/w of the chitosan -SOS combination (AAAS 82) was added to the gel solution. The mixtures were mixed with...

...as experimental animals because pigs have proven to be a good model for assessment of wound healing in humans.

Five-ten female SPF pigs (body weight of about 25-50 kg) from...before washing with soap and water followed by disinfection with 70% ethanol. Before surgery the skin of the back will be rinsed with sterile 0.9% saline.

Circular full thickness wounds will be prepared surgically (diameter 20 mm). Ten wounds (5 on each site of the midline) will be prepared on each pig. A schematic illustration of number and localization of wounds are given below.

nose

I 6  
2 7  
8  
9  
10

Tail

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Distribution of test articles on wounds .

pig No. 1 pig No.2 pig No. 3 pig No. 4 pig No.5...

...9 Control

10 Control 10 TA4 10 TA-3 10 TA-2 10 TA-1

Wound dressings are as follows.

TA-1, TA-2, TA-3, TA-4 see above, Control no treatment

Tracing

After wounding on day 0 and on day 3, 6, 10 and 12, each wound will be traced i.e. a drawing of the margin of the wound on a sterile transparent film using a thin pencil. On day 3, 6, 10 and 12 the epithelial rim will also be traced.

Treatment

After wounding each of the test dressings will be applied to the wounds . The allocation of treatments is described above. This treatment scheme secures and even distribution of the treatments to the different wound positions spread over the five pigs.

After treatment the wound can be covered with Tagaderm and thereafter gauze (4 layers) which will be fixed with 2.5 cm Scanpor Tape. Subsequently, the test...

...be covered/fixed with Fizionet. Finally the pig will be dressed in Fizionet elasticated net dressing .

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Every day or every second day the applied dressings will be removed and new dressings and drug composition will be applied according to the same procedure used on day 0...

...procedure.

Observations

Body weight

The animals will be weighed on arrival, on the day of wounding and on the day of ...Daily inspections

The animals will be inspected at least once daily for signs of ill health . The dressings will be inspected and any detached dressing reapplied or, if necessary, redressed with the same type of dressing .

All observations and actions will be recorded.

Each wound will be observed and evaluated daily. The grade of inflammation and exudation will be evaluated...

...article in the Photos The following photos will be taken.

Overview photo of all the wounds

A close-up photo of each wound separately.

Estimation of wound exudate

Estimating the amount of exudate using a score 0

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0 = No exudate

1 = Small amount

2 = Medium amount

3 = High amount

Estimation of infection/ irritation

Estimating erythema and/or oedema in the skin surrounding the wounds .

Tracing of wounds (for Planimetric calculations)

Drawing on the transparent sterile film of the outer margin of the wounds . Additionally the epithelial run will be drawn when appearing.

Terminal observations

Twelve days after wounding (day 12) the animals will be anaesthetized by a stunning gun and sacrificed by a cut of the vessels to a forelimb.

At termination each wound will be excised with a full thickness cut and at least a 5 mm margin of normal skin around the wound .

Each wound will be attached to a piece of cardboard with one piece of gauze in between and fixed in neutral 4% buffered formaldehyde. Care will be taken in order to secure that animal number, wound number and position can be identified.

Histopathology

Two tissue samples (sample 1 and 2) from each wound will be paraffin embedded and sections cut at nominal thickness of 5 µm will be...

...Planimetry

At photo copy of each tracing sheet is made and the area of each wound and epithelial rim is determined by video planimetry, using a video camera (Kafpa CF8) and...

...Methylparahydroxybenzoate 1 g

Glycerol 85% 40 g

Sorbitol 70 g

Purified water 724 g

3. Chitosan -SOS 100 g

1 is melted together at about 70°C and 2 - which immediately...as e.g. DecubalO cream (added from about 0.1% to about 40% w/w chitosan -SOS).

EXAMPLE10

Preparation of a gel - 1

0.5% w/v methyl cellulose

1% w/v chitosan

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2% w/w chitosan -SOS combination (pulverized)

2% w/v glycerol

optionally a suitable preservative in an appropriate concentration

up to 100% w/v purified water, adjusted to pH 5.6

200 ml chitosan (2% w/v) was mixed with 100 ml of methyl cellulose (2% w/v) and then 8 ml of glycerol was added under stirring. 8 g chitosan -SOS combination was dispersed in the highly viscous solution and the volume adjusted to 400...

...CL 210

2 g methyl cellulose

200 ml purified water, pH 5.5

10 g chitosan -SOS combination (premilled)

0.2 g methylparahydroxybenzoate



The methylparahydroxybenzoate was dissolved in 190 ml water...  
...hours at a shaking table at room temperature to obtain a homogeneous  
viscous solution. The **chitosan** -SOS combination (pulverized) was  
dispersed in the viscous phase.

Other gels have also been prepared containing **chitosan** -SOS combination  
in various concentrations (1-5% w/w). The gels are based on the...

...of the polymer is in a range of about 2-3% w/w. In general **chitosan** ,  
SOS, a **chitosan** -SOS combination and a physical blend of **chitosan** and  
SOS,  
SUBSTITUTE SHEET (RULE 26)  
respectively, is/are added in a concentration range of about 1-10% w/w.  
The following results have been obtained.

**Chitosan** -SOS: suitable suspension gels are formed; up to about 40% w/w  
of **chitosan** -SOS  
can easily be incorporated

**Chitosan** : increases the viscosity of the gel, but a suitable gel can be  
prepared by

adjusting the concentration of **chitosan** and polymer

SOS: In concentrations above 3-5% w/w of SOS the gel separates

**Chitosan** + SOS (blend): Most likely **chitosan** -SOS is formed in an  
uncontrollable manner.

Precipitation of **chitosan** -SOS has been observed. The gels obtained were  
not suitable for medicinal application purposes as...

...following constituents.

95 g polyethylene (DLS - Danish Drug Standards)

855 g paraffin oil

50 g **chitosan** -SOS

Polyethylene is dissolved in ...mixture is cooled with a speed of about  
2°C/min under stirring (ointment basis). **Chitosan** -SOS (premilled) is  
sieved through a sieve 125 immediately before the combination is  
dispersed in...

...prepared containing the following constituents.

0.5 % w/v methyl cellulose

1.0 % w/v **chitosan** -SOS combination (pulverized)

2.0% w/v glycerol

water, pH adjustment to about pH 5.6

The ointment is made by mixing 100 ml of an aqueous dispersion of the  
**chitosan** -SOS combination (2% w/v) in a mixer with 50 ml methyl cellulose  
(2% w/v).

...obtained has a highly viscous consistency.

#### EXAMPLE 14

Preparation of powders for application e.g. to wounds

A.

20 g **chitosan** -SOS combination (very fine powder)

80 g lactose

The powder was prepared by mixing the **chitosan** -SOS combination with the  
lactose using a mortar. The powder can directly be applied to the damaged  
tissue or it may be covered by a **dressing** or adhesive.

B 1.

40% w/w chitosan -SOS combination (very fine powder)  
60% w/w sodium alginate

B 2.

20% w/w chitosan -SOS combination (very fine powder)  
80% w/w sodium alginate

C.

20% w/w chitosan -SOS combination (very fine powder)  
SUBSTITUTE SHEET (RULE 26)  
80% w/w collagen

D.

30% w/w chitosan -SOS combination (very fine powder)  
70% w/w lactose

The powders B-D were prepared...

...manner to the method described under A. The powders may also be covered by a dressing or an adhesive.

#### EXAMPLE15

Preparation of a suspension spray

Chitosan -SOS combination 100 mg

Glucose 475 mg

EDTA disodium 1 mg

Microcrystalline cellulose 125 mg...

...NaOH to adjust pH

Purified water ad 5 ml

#### EXAMPLE16

Preparation of a topical suspension

Chitosan -SOS 5.00% w/w

Water 76.97% w/w

Isopropyl alcohol 10.00% w...

...W

Paraffin oil DAB 9 7.0% w/w

Arlamol E 3.0% w/w

Chitosan -SOS 25.0% w/w

Magnesium stearate 1.0% W/W

Tocopheryl acetate

(a-tocopherol...

#### Claim

... of the preceding claims, wherein the first compound is selected from the group consisting of chitosan, chitosans obtained by deacetylated of chitin to various degrees of deacetylation, chitosan derivatives, glycosaminoglycans including chondroitin, chondroitin sulfate, hyaluronic acid, dermatan sulfate and keratan sulfate; aminated dextrans including DEAE-dextran; aminated starch, aminated glycogen, aminated cellulose...

...11 A combination according to any of the preceding claims, wherein the combination has a healing effect on wounds in vitro when tested as described herein.

12 A combination according to any of the...

...A combination according to any of the preceding claims, wherein the first compound is a chitosan.

19 A combination according to claim 18, wherein the **chitosan** has a molecular weight in a range of about 3,000 to about 1,500,000 daltons.

20 A combination according to claim 18, wherein the **chitosan** has a degree of deacetylation of at the most 100% such as at the most 99%, 95%, 90%, 85%, or 80%.

21 A combination according to claim 18, wherein the **chitosan** has a degree of deacetylation in a range of about 10-90% such as about...the thus formed combination.

39 A method for stabilizing a tissue repair agent in a **injured** tissue comprising applying a combination according to any of claims 1-27 on the **injured** tissue.

40 A combination of a first compound of an oligo- or polysaccharide containing aminosugar...lisinopril; antihyperlipoproteinemic agents including: acifran, acipimox, ciprofibrate, clinofibrate, clofibric acid, pravastatin sodium, fluvastatin, gemfibrozil, meglutol, **nicotinic acid**, and oxiniacic acid; antiamebic agents including: Thiocarbamizine; luteolytic agents including: Tiaprost; antiulcerative agents including: arbaprostil...of claims 40-46, wherein the first compound is selected from the group consisting of **chitosan**, **chitosans** obtained by deacetylated of **chitin** to various degrees of deacetylation, **chitosan** derivatives, glycosaminoglycans including chondroitin, chondroitin sulfate, hyaluronic acid, **dermatan** sulfate and keratan sulfate; aminated dextrans including DEA-E-dextran; aminated starch, aminated glycogen, aminated...

...A combination according to any of claims 40-47, wherein the first compound is a **chitosan**.

49 A combination according to claim 48, wherein the **chitosan** has a molecular weight in a range of about 3,000 to about 1,500,000 daltons.

50 A combination according to claim 48, wherein the **chitosan** has a degree of deacetylation of at the most 100% such as at the most 99%, 95%, 90%, 85%, or 80%.

51 A combination according to claim 48, wherein the **chitosan** has a degree of deacetylation in a range of about 10-90% such as about...

Set	Items	Description
S1	723061	BANDAG? OR GAUZ? OR COMFEEL? OR PATCH? OR DRESSING? OR COMPRESS?? OR BAND AID? OR BAND() (AID OR AIDS) OR PAD OR PADS
S2	2870626	MAIM? OR SCRATCH? OR SCRAP? OR ABRASION? OR TRAUMA? OR INJURY? OR WOUND? OR LACERAT? OR BURN? OR IRRITATION?
S3	82162	CHITOSAN? OR C8H13NO5 OR "1398-61-4" OR 1398()61()4 OR CHITIN OR CHITINDEACETYLAT? OR GLUCOSAMINE(3N)POLYSACCHARID? OR -ACHITIN OR ACETYL?(2N)GLUCOSAMIN?
S4	153659	(ASCORBAT? OR ASCORBIC?) (2N) (SALT? OR ACID? OR SODIUM? OR -MINERAL? OR CALCIUM? OR MANGANES? OR MAGNESIUM?) OR VITAMINC -OR VITAMIN()C OR C6H8O6 OR "50-81-7" OR 50()81()7
S5	114893	NIACINAMID? OR NIACIN? OR NICOTINIC()ACID? OR NICOTINAMID? OR C6H5N2O OR C6H6N2O OR "98-92-0" OR 98()92()0 OR "59-67-6" -OR 59()67()6 OR (PYREDENE? OR PYRIDINE?) (2N) (CARBOXYLIC? OR CARBOXAMID?) OR VITAMINB3 OR VITAMIN() (B3 OR B()3)
S6	8090327	HEAL? OR CURE?? OR CURING OR SKIN? OR DERMA? OR DERMI? OR -DERME? OR DERMO?
S7	6	S3 AND S4 AND S5
S8	0	S7 AND S1
S9	1	S7 AND S6
S10	6	S7 OR S9
S11	0	S1 AND S3 AND S4:S5
S12	1054	S1 AND S3
S13	5	S10 AND PY<2002
S14	1	RD (unique items)

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S3	2878	CHITOSAN? OR C8H13NO5 OR "1398-61-4" OR 1398()61()4 OR CHITIN OR CHITINDEACETYLAT? OR GLUCOSAMINE(3N)POLYSACCHARID? OR -ACHITIN OR ACETYL?(2N)GLUCOSAMIN?
S4	28092	(ASCORBAT? OR ASCORBIC?) (2N) (SALT? OR ACID? OR SODIUM? OR -MINERAL? OR CALCIUM? OR MANGANES? OR MAGNESIUM?) OR VITAMINC -OR VITAMIN()C OR C6H8O6 OR "50-81-7" OR 50()81()7
S5	9767	NIACINAMID? OR NIACIN? OR NICOTINIC()ACID? OR NICOTINAMID? OR C6H5N2O OR C6H6N2O OR "98-92-0" OR 98()92()0 OR "59-67-6" -OR 59()67()6 OR (PYREDENE? OR PYRIDINE?) (2N) (CARBOXYLIC? OR CARBOXAMID?) OR VITAMINB3 OR VITAMIN() (B3 OR B()3)
S6	4275298	HEAL? OR CURE?? OR CURING OR SKIN? OR DERMA? OR DERMI? OR -DERME? OR DERMO?
S7	24	S3 AND S4 AND S5
S8	14	S7 AND S1
S9	14	S8 AND (S2 OR S6)
S10	14	S8:S9
S11	11	S10 AND PY<2002
S12	10	RD (unique items)

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L2 102347 S (ASCORBAT? OR ASCORBIC?) (2N) (SALT? OR ACID? OR SODIUM? OR M  
L3 48698 S NIACINIMID? OR NIACIN? OR NICOTINIC? (W) ACID? OR NICOTINAMID  
L4 43 S L1 AND L2 AND L3  
L5 5 S L4 AND (BANDAG? OR GAUZ? OR COMFEEL? OR PATCH? OR DRESSING?

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AB The present invention relates to a novel composition for efficiently releasing hydrophilic or water-soluble skin care actives from an oleaginous composition

The

substantially oleaginous composition of the present invention comprises: (1) at least one skin care active; (2) a release agent having an HLB of at least about 3; and (3) a hydrophobic barrier protectant. The novel release composition may be topically applied to skin using a dispensing means such as an absorbent article, a wipe, a bandage, a pad, a canister, a stick, an aerosol dispenser, a sprayer, and the like. For example, a release composition was formulated containing hexamidine

diisethionate

0.1, Beheneth-10 6.3, Petrolatum 72.6, behenyl alc. 17.7, and fumed silica 3.3 %, then deposited on a top sheet of an absorbent article.

ACCESSION NUMBER: 2004:282815 HCAPLUS

DOCUMENT NUMBER: 140:309487

TITLE: Skin-protecting compositions to be delivered from absorbent articles

INVENTOR(S): Osborne, Scott Edward; Deckner, George Endel; Klofta, Thomas James; Vega, Victor Nicholas

PATENT ASSIGNEE(S): The Procter & Gamble Company, USA

SOURCE: U.S., 14 pp., Cont.-in-part of U.S. Ser. No. 41,266, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

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US 6716441	B1	20040406	US 1999-466343	19991217
ZA 9902000	A	19990913	ZA 1999-2000	19990311
TR 200002601	T2	20001221	TR 2000-200002601	19990311
WO 2001043717	A1	20010621	WO 2000-US33741	20001213
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP 1237535	A1	20020911	EP 2000-984288	20001213
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2003516955	T2	20030520	JP 2001-544656	20001213
PRIORITY APPLN. INFO.:			US 1998-41266	B2 19980312
			US 1999-466343	A 19991217
			WO 2000-US33741	W 20001213

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The present invention is directed to compns. and methods for the enhancement of iron uptake or the treatment of iron deficiency by enhancing the rate and extent of dissoln. in a subject in need thereof. The composition contains at least two iron-providing materials in a single dosage form wherein at least one of the iron-providing materials contains a modified release mechanism, matrix, or coating, selected from, e.g., cellulose derivs., gelatin, polymethacrylates, polyvinyl alc., and acrylic resins. The iron-providing materials included within the composition have

*see claim 1 of US version*

different rates of release. Following administration to the animal, the iron-providing materials are released in the gastrointestinal tract over a period of up to 24 h. For example, the iron salt (ferrous fumarate) 20 mg was added to a melted wax or fatty acid in the molten form, the material was allowed to solidify, the solidified product was milled and mixed with other ingredients, i.e., di- $\alpha$ -tocopheryl acetate 30 IU, calcium ascorbate 60.0 mg, thiamine mononitrate 3.0 mg, riboflavin 3.4 mg, pyridoxine monohydrochloride 50.0 mg, cyanocobalamin 12.0  $\mu$ g, niacinamide 20.0 mg, folic acid 1.0 mg, calcium carbonate (Destab 38% Ca) 200.0 mg, iron (carbonyl iron, 70%) 10.0 mg, cupric oxide 2.0 mg, zinc oxide 15.0 mg, and magnesium oxide 100.0 mg.

The resulting composition was compressed into tablets.

ACCESSION NUMBER: 2003:796116 HCAPLUS  
DOCUMENT NUMBER: 139:296990  
TITLE: Modified-release iron compositions  
INVENTOR(S): Hermelin, Marc S.; Grimshaw, Michael  
PATENT ASSIGNEE(S): USA  
SOURCE: U.S. Pat. Appl. Publ., 12 pp.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

LATE  
DATE

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003190355	A1	20031009	US 2002-115892	20020405
WO 2003086321	A2	20031023	WO 2003-US9023	20030326
WO 2003086321	A3	20040513		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 2002-115892 A 20020405

L5 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN  
AB An adhesive patch including a flexible backing having a front side and a back side and a cosmetic formulation positioned on and/or in at least a portion of the front side of the backing is provided. The cosmetic formulation includes a cosmetic agent, a solvent, a skin absorption enhancer, and at least one of a pressure sensitive adhesive and a polymer. For example, an adhesive patch contained polyacrylamide 13.0%, glycerin 53.5%, water 19.0%, vitamin A palmitate 0.25%, grape seed oil 0.5%, fragrance 0.25%, ammonium lactate 1.0%, propylene glycol 4.0%, diethylene glycol Et ether 5.0%, emulsion adhesive 3.0%, and preservative 0.5%.

ACCESSION NUMBER: 2003:610222 HCAPLUS  
DOCUMENT NUMBER: 139:169003  
TITLE: Cosmetic patch comprising a pressure sensitive adhesive and a polymer  
INVENTOR(S): Rolf, David; Buseman, Teri; Cooke, Dede  
PATENT ASSIGNEE(S): Lectec Corporation, USA  
SOURCE: PCT Int. Appl., 76 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1

LATE  
DATE



## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003063817	A1	20030807	WO 2003-US2425	20030128
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003152610	A1	20030814	US 2002-60060	20020128
PRIORITY APPLN. INFO.:			US 2002-60060	A 20020128
REFERENCE COUNT: 6		THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT		

L5 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

AB A wound **dressing** includes a first layer located adjacent the wound and which comprises a material that is bioabsorbable, porous and adapted for serving as a scaffold for cell attachment and proliferation; and a second layer which is in contact with the first layer and which comprises an absorbent, gel forming material adapted for serving as a barrier to cell adhesion and penetration. A method of treating a wound with the **dressing** is also disclosed. Preparation of a scaffold material having poly(lactic acid) fibers coated with hyaluronate and chitosan niacinamide ascorbate is disclosed.

ACCESSION NUMBER: 2002:616416 HCAPLUS

DOCUMENT NUMBER: 137:174999

TITLE: Bioabsorbable wound **dressing** bioabsorbable and gel-forming layers

INVENTOR(S): Greene, Sharon L.; Ambrosio, Archel A.; Matthews Kaylor, Rosann M.; Soerens, Dave A.

PATENT ASSIGNEE(S): Kimberly-Clark Worldwide, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 17 pp.  
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

*PROV. FILE 8*  
*DATE*  
*29 DEC*  
*2000*

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002111576	A1	20020815	US 2001-26292	20011219
WO 2002072163	A1	20020919	WO 2001-US49405	20011221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1345635	A1	20030924	EP 2001-993315	20011221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			US 2000-259120P	F 20001229
			US 2001-26292	A 20011219
			WO 2001-US49405	W 20011221

L5 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

AB The heterogeneous acid decrystn. of aminopolysaccharides, especially **chitosan**, using diluent, organic acid, and H<sub>2</sub>O, provides novel salts and covalent derivs. while avoiding processing difficulties encountered with aqueous processing. The products are useful in fluid separation, personal care products, and biomedical applications. **Chitosan** (80% deacetylated) was ground and slurried in H<sub>2</sub>O-Me<sub>2</sub>CO, and itaconic acid was added as a powder and the slurry was stirred for 3 h. The slurry was allowed to settle, supernatant was decanted, Me<sub>2</sub>CO was added, and the polymer was collected by filtration; the mass gain of chitosonium itaconate was 0.30. Chitosonium itaconate was dissolved in hot H<sub>2</sub>O, the solution cooled, sulfanilamide was added, and a film was cast and cured at 100° for 18 h. Although the film was insol. in water, >95% of the sulfanilamide was extracted from the film in H<sub>2</sub>O after 30 min.

ACCESSION NUMBER: 1989:179564 HCAPLUS

DOCUMENT NUMBER: 110:179564

TITLE: Preparation of aminopolysaccharide derivatives, especially chitosonium salts, by acid decrystallization, and their medical, cosmetic, and liquid separation uses

INVENTOR(S): Partain, Emmett Malone, III; Brode, George Lewis, II

PATENT ASSIGNEE(S): Union Carbide Corp., USA

SOURCE: PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8707618	A1	19871217	WO 1987-US1246	19870602
W: JP, US				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
EP 271551	A1	19880622	EP 1987-904163	19870602
EP 271551	B1	19961030		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 63503466	T2	19881215	JP 1987-503854	19870602
JP 07076241	B4	19950816		
AT 144781	E	19961115	AT 1987-904163	19870602
CA 1283655	A1	19910430	CA 1987-539050	19870608
US 4929722	A	19900529	US 1988-189312	19880203
PRIORITY APPLN. INFO.:			US 1986-871381	19860606
			WO 1987-US1246	19870602

*see in  
US version:  
Col. 6, 47+;  
Col. 18, 24+;  
Claims  
8, 9.*

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